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AGRANULOCYTOSIS (MALIGNANT NEUTROPENIA)

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PHILADELPHIA

It is reasonable to believe that as man advances in civilization new diseases will arise in response to new environmental phenomena.

Most authorities agree that agranulocytosis, or malignant neutropenia, has not been described in past years because it is a comparatively recent disease. Although blood counts have been taken for more than fifty years in most hospitals, not one case of this condition was reported in these institutions.

A thorough review gives Senator [1] the credit of the first report in the literature. In 1888, he reported four cases of an unusual type of pharyngitis, all resulting in death. The clinical picture closely followed malignant neutropenia. Pepper,[2] in an excellent article on this subject, stated that Mackenzie [3] gave Gubler,[4] in 1857, and Trousseau,[5] in 1865, credit for describing the symptomatology of this condition and differentiating it from other anginas, including diphtheria. It was, however, not until 1902, when Brown [6] made the first report of a fatal case of acute primary infectious pharyngitis with leukemia, that interest of a decided character was manifested in this disease. Several later reports of cases made at seemingly long intervals caused considerable discussion. But it was not until Schultz [7] reported four cases in 1922, at which time he described the clinical syndrome and attached the term "agranulocytosis," that stimulated interest became acutely pronounced, with the reporting of many cases from various sources and the propounding of many theories as to the pathogenesis and treatment.

Read before the Section on Laryngology, Otology and Rhinology at the Eighty-Fifth Annual Session of the American Medical Association, Cleveland, June 14, 1934.

1. Senator, H.: Ueber acute infectiöse phlegmonöse Pharyngitis, München. med. Wchnschr. **35**:47, 1888.
2. Pepper, O. H. P.: The History of Agranulocytic Angina, J. A. M. A. **97**:1100 (Oct. 10) 1931.
3. Mackenzie, Morell: A Manual of Diseases of the Throat and Nose, London, J. and A. Churchill, 1880.
4. Gubler: Arch. gén. de méd. **9**:513, 1857.
5. Trousseau: Clin. méd. de l'Hôtel-Dieu, Paris, 1865, p. 324.
6. Brown, P. K.: Am. Med. **3**:649 (April) 1902.
7. Schultz, W.: Deutsche med. Wchnschr. **48**:1495, 1922.

DEFINITION

Malignant neutropenia is a disease characterized by marked diminution in the number of circulating neutrophils. This in turn is followed by: no infection, local infection or general infection. The disease has a clearcut pathologic picture and a definite clinical course, with signs, symptoms and a blood picture which are as characteristic as those of pernicious anemia.

ETIOLOGY

The etiology is still speculative, but several pertinent observations have been made recently:

1. Early in the study of the disease a bacterial agent was looked for. Lovett [8] isolated Bacillus pyocyaneus from the mouths of patients ill with the disease and injected it into rabbits. She obtained leukopenia, but on further observation it was noted that a large number of normal rabbits which had not received injections showed the same condition, and efforts to isolate a bacterial agent were unsuccessful.

2. A more philosophic view of the infectious theory was expressed by Kracke,[9] who stated that the disease may be due to some toxic agent depressing to the myeloid portion of the bone marrow, resulting in lowered resistance and overwhelming infection by any or every organism in the body.

3. The condition may be produced by spirilla found in the mouth, since many cases begin after the extraction of a tooth or during oral infection. However, the condition may be present because the patients have low resistance and chronic neutropenia.

4. That dead bacteria and bacterial toxins depress leukocyte counts was demonstrated by Bromberg and Murphy,[10] and some cases have occurred following the use of typhoid vaccine.

5. Leukopenia is a part of, and often follows, influenza and agranulocytosis has also followed this disease.

6. Arsenicals, the roentgen rays and radium produce leukopenia, and agranulocytosis has followed their use; strangely, they have also been employed for its treatment.

7. Pepper [2] and others have suggested that an allergic reaction of sensitive bone marrow may be involved in the disease.

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8. Lovett, Beatrice: Agranulocytic Angina, J. A. M. A. **83**:1498 (Nov. 8) 1924.

9. Kracke, Roy: (*a*) A Review of Granulocytopenia (Agranulocytosis), J. Lab. & Clin. Med. **17**:993, 1932; (*b*) Experimental Production of Agranulocytosis, Am. J. Clin. Path. **2**:11, 1932; (*c*) J. Lab. & Clin. Med. **16**:93, 1932.

10. Bromberg, L., and Murphy, P.: Agranulocytic Angina Following Prophylactic Typhoid Vaccination, J. A. M. A. **92**:1266 (April 13) 1929.

8. Benzene is the only chemical which was shown for a number of years to be capable of producing neutrophilic depression to the point of agranulocytosis. Alice Hamilton [11] first demonstrated this in rabbits. Simonds and Jones showed that immune bodies were decreased in rabbits treated with benzene.

Within the last two years Kracke [9b] has shown the production of the condition with related organic compounds—salicylic acid and hydrochinone.

9. Focal infection has been suggested.

In cases reported from many sources an important factor is the ratio of the sex of those affected. Nearly 80 odd per cent are females, and those whose symptoms have been present for any length of time give conclusive evidence that the condition is much worse at or before the menstrual period. This suggests that research should be made along this line and the sex hormones considered along with the other etiologic factors. Thompson,[12] in reviewing forty cases which were studied in his clinic, suggested a possible temporal correlation between the onset of the neutropenia and the onset of menstruation. This coincides with the known predominance of the condition in women. He also reported a case of cyclic neutropenia in a male, which has been carefully followed through the patient's life from the early age of 2½ months until his present age of 25 years. The early history was reported by Rutledge, Hansen-Pruss and Thayer.[13]

Eighty per cent of all the reported cases in women have occurred within the menstrual age, or in women less than 45 years old, and the onset of the subjective symptoms occurred within a day or two of the onset of the regular menstrual period.

That a definite relationship exists in some cases between the hormones associated with menstruation and neutropenic episodes seems conclusive.

EXPERIMENTAL EVIDENCE AND PRODUCTION

The blood count shows diminution or absence of the granular white cells, and Kastlin [14] asked whether the disappearance of cells is due to (1) increased peripheral destruction, (2) abnormal distribution of cells or (3) failure of development of cells. The first factor is probably not causative, because the spleen does not enlarge as it would in response

11. Hamilton, Alice: Growing Menace of Benzene (Benzol) Poisoning in American Industry, J. A. M. A. **78**:627 (March 4) 1922.

12. Thompson, W. P.: Observations on the Possible Relation Between Agranulocytosis and Menstruation, with Further Studies on Case of Cyclic Neutropenia, New England J. Med. **210**:176 (Jan. 25) 1934.

13. Rutledge, B. H.; Hansen-Pruss, O. C., and Thayer, W. S.: Bull. Johns Hopkins Hosp. **46**:369, 1930.

14. Kastlin, G. J.: Agranulocytic Angina, Am. J. M. Sc. **173**:799, 1927.

to destruction of cells, and one fails to find the disintegrating element. In regard to the second possibliity, there is no proof that the granular cells alone are withdrawn into the capillary beds. In regard to the third possibility, biopsy of tissue from patients and necropsy on man and experimental animals show a definite change in the myeloid tissue, with microscopic evidence of little or no granulocytogenesis.

Kracke [9c] produced the disease in rabbits. He gave them 1 cc. each of olive oil and benzene subcutaneously and within from a week to ten days produced typical agranulocytosis.

He also experimented with acetphenetidin, amidopyrine, a mixture of amidopyrine and barbital, dial, resorcinol, pyrocatechol, orthocresol, metacresol, paracresol and phenol given by subcutaneous and intravenous routes, but they did not apparently affect the leukocytes.

Recently, Madison and Squier [15] were able to produce fairly typical agranulocytosis in a rabbit that was given 20 grains (1.3 Gm.) of a barbital derivative daily, by mouth. The rabbit began to show neutropenia twenty-five days after the first administration and died five days later, on the thirtieth day of treatment, with agranulocytosis and moderate anemia.

How much more susceptible man is than the rabbit is still doubtful, but many recent reports suggest that he is far more sensitive to the coal tar drugs.

INCIDENCE

The disease has been reported chiefly in middle-aged women, but persons of both sexes and all ages are susceptible. It does not appear to be highly infectious and occurs sporadically.

Most of the literature concerning it is American and German. It is apparently infrequent in France, rare in Italy and almost unknown in the Orient.

The countries in which the incidence is highest use the largest amounts of organic compounds, aniline dyes and coal tar drugs.

It is not limited to any one class or occupation, although recently Madison and Squier,[15] Randall [16] and Hoffman, Butt and Hickey [17] reported cases in which the coal tar drugs seemed to be directly responsible for the onset and course of the illness. The disease was found in physicians, nurses, druggists and patients under the care of physicians, all of whom had the coal tar drugs rather freely available.

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15. Madison, F. W., and Squier, T. L.: Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. **102**:755 (March 10) 1934.

16. Randall, C. L.: Severe Granulopenia Following the Use of Barbiturates and Amidopyrine, J. A. M. A. **102**:1137 (April 7) 1934.

17. Hoffman, A. M.; Butt, E. M., and Hickey, N. G.: Neutropenia Following Amidopyrine, J. A. M. A. **102**:1213 (April 14) 1934.

It is unfortunate that rhinolaryngologists are not consulted earlier in these cases, not only to improve treatment, but also to note symptoms which may later disappear or be overclouded by others which are more prominent.

SYMPTOMS

The patients are prostrated, lack all initiative and ambition and have continuous and pronounced malaise, with blanched skin, more dry and wrinkled than normal skin. These symptoms are out of all proportion to the physical signs. The history, which is given by the patient or, more frequently, by a member of the family, is that the patient has for some time been easily fatigued, short of breath, compelled to get more rest than formerly and irritable, has shown lack of interest and has had slight fever at some time during the day. There is a history of several attacks of tonsillitis or infection of the oral cavity. As the condition progresses the elevation in temperature increases, and chilly sensations or a severe chill may be the initial symptom of the fulminating cases.

Rhinolaryngologists must be made cognizant of the fact that all the systemic symptoms and signs, including the blood picture, have been present for some time before the particular local lesions (those pertaining to the mouth, nose and throat) were manifested. These lesions are found in the mouth, on the tonsillar surface and the anterior pillars of the fauces or along the gingival margins. They are light grayish or white ulcerative patches and may extend to the uvula, tongue or pharyngeal membrane. In a number of cases reported and in two of my own, tumefaction or bulging in the peritonsillar region, simulating abscess formation, was noted, but no fluctuation was noticeable, nor did an incision elicit pus. There is likewise a similarity in the white or dirty gray color of the lesions and their ulcerative character.

LABORATORY STUDIES

The blood picture is so characteristic that there is little likelihood of diagnostic error. With the exception of the abortive forms, the total leukocyte count is commonly less than 2,000 cells per cubic millimeter, and in the fulminating forms this may fall as low as 200, as the result of the marked neutropenia. In the latter form the blood is frequently devoid of granulocytes, while in the chronic and recurrent forms the immature granulocytes may constitute from 20 to 30 per cent of the cells present. Due consideration must be given to a terminal rise in the number of immature granulocytes, noted by Krumbhaar [18] in his observations on the effect of gas poisoning. This is occasioned by the liberation of the remaining immature granulocytes into the blood stream,

18. Krumbhaar, E. B.: The Rôle of the Blood and the Bone Marrow in Yellow Cross Gas (Mustard Gas) Poisoning, J. M. Research **40**:497, 1919.

with the destruction of the granulopoietic tissue. This phenomenon Krumbhaar called the "myelocytic crisis." Schilling,[19] similarly, believes that the immature neutrophils, that is, the stab and juvenile forms, are frequently present in increased numbers in patients in whom there is almost complete necrosis of the bone marrow as the result of the gradual discharge of the remnants of the immature cells into the circulating blood. The striking feature of this reaction is the progressive decrease in the total number of granulocytes, which Schilling designates as the degenerative shift to the left. Fried and Dameshek,[20] in their work with Salmonella suipestifer in rabbits, not only confirmed the hypothesis of the degenerative shift of the granulocytes but observed a regenerative shift as well. The latter picture is associated with the recovery phase of benign and recurrent forms of neutropenia, showing the progressive rise in the neutrophilic leukocytes in the regenerative states of the bone marrow.

Beck,[21] citing the work of Sabin,[22] called attention to the normal rhythmic liberation of the cells into the circulating blood. The lymphocytes present an early relative increase in number, and as the condition progresses absolute lymphopenia develops. Mononuclear leukocytes as a rule present little change; in the acute and fulminating forms they may at times show an absolute decrease. In the recovery phase, which has been previously noted, the mononuclear leukocytes are increased in number and are associated with the appearance of macrophagocytes or histiocytes in the blood stream. Fried and Dameshek [20] reported two cases showing this reaction of defense on the part of the reticuloendothelial system. The erythrocytes fail to show any change in the early stages, while in the chronic forms and in those in which the disease extends over a period of ten days the picture is characteristic of secondary anemia following any other cause. The cells are achromic, and the color index is less than 1. The platelets appear normal. Thrombocyptopenia is frequently associated with aplasia of the bone marrow following the use of drugs containing the benzine radical.

The results of blood cultures are variable. The cultures are positive in approximately from 10 to 15 per cent of the cases. The organisms isolated from the blood stream include the pneumococcus, Streptococcus

19. Schilling, V.: The Blood Picture, ed. 7, St. Louis, C. V. Mosby Company, 1929, p. 197.

20. Fried, B. M., and Dameshek, W.: Experimental Agranulocytosis; Infection of Rabbits with Salmonella Suipestifer by Way of the Blood Stream, Arch. Int. Med. **49**:94 (Jan.) 1932.

21. Beck, R. C.: Benign and Malignant Neutropenia; Present Status of Knowledge of This Condition, with Report of Four Cases, Arch. Int. Med. **52**: 239 (Aug.) 1933.

22. Sabin, F. R.: Physiol. Rev. **8**:191, 1928.

haemolyticus, Streptococcus viridans, Bacillus coli-communis and B. pyocyaneus. The same group of bacteria is present in the local ulcerative lesions, in addition to staphylococci and Vincent's organism. In one case reported by Roberts and Kracke [23] Str. haemolyticus was isolated from the blood stream, sputum, urine, feces, the multiple abscesses and local lesions. These organisms have been obtained from the blood in the vena cava and heart. Postmortem blood cultures are as frequently negative as otherwise. Piette,[24] in a detailed histologic study of tissue removed at autopsy ten hours after death, observed bacterial emboli in the liver, spleen, kidney, stomach and suprarenal glands. No bacteria have been recovered from the bone marrow.

Examination of the urine is of little diagnostic value. The urine contains varying amounts of albumin, which range from a slight trace to a heavy cloud. Light granular and hyaline casts are present inconsistently. Leukocytes are likewise an inconstant observation.

PATHOLOGY

The pathologic picture varies greatly, depending on the duration, severity and potency of the nocuous agent and the resistance of the patient. The local lesions in the mouth, stomach, intestine, anus and vagina range from a minute superficial ulcer to widespread and extensive gangrene. They show the same histologic picture, characterized by the absence of the granulocytes, and consist of a central area of necrosis surrounded by an indefinite zone of lymphocytes and endothelial leukocytes. The strange feature, however, is the complete absence of neutrophilic leukocytes. Piette thinks that the lesions are due primarily to occlusion of the smaller vessels by bacterial emboli. The bacteria reach the body by some unknown portal of entry, destroy the granulocytes, multiply and give rise to the emboli.

In the acute fulminating cases the myocardium is flabby, and the changes are those of acute toxic degeneration. The liver is somewhat enlarged, showing cloudy swelling. The general structure is, however, usually well preserved. The Kupffer cells are hyperplastic and contain varying amounts of blood pigment. The hepatic cells are the site of fatty degeneration, with an occasional focus of necrosis and perivascular lymphocytic infiltration. The cells are filled with bile pigment, while the bile capillaries are frequently laden with casts. The spleen shows decided structural change, in which the reticulo-endothelial cells undergo extensive proliferation, occupying 90 per cent of the entire splenic substance.

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23. Roberts, S. R., and Kracke, Roy: Agranulocytosis; Report of a Case, J. A. M. A. **95**:780 (Sept. 13) 1930.

24. Piette, E. C.: Histopathology of Agranulocytic Angina, J. A. M. A. **84**: 1415 (May 9) 1925.

The sinuses are almost entirely free from the cellular elements, with the exception of an occasional lymphocyte and plasma cell. The follicles are small and atrophic, and the pulp is composed of small lymphocytes, scattered plasma and reticular cells. The reticular cells are frequently enlarged and contain two or more nuclei of irregular shape, resembling giant cells. Anemic infarcts are not uncommon. The lymph nodes, especially the submaxillary, peribronchial and mesenteric nodes, are similarly enlarged. The follicles are atrophic, and the germinal centers contain only mature cells. The reticulo-endothelial cells show evidence of proliferation.

The kidneys may show comparatively little change, while at times the picture is that seen in acute nephritis. Marked degenerative changes occur in the parenchyma. The cells of the convoluted tubules are necrotic and stain poorly. The lumens contain hyaline casts. The stomach frequently shows widespread active congestion of its mucous membrane; the superficial lesions extend to the muscularis mucosae and consist of a central area of necrosis surrounded by a zone of lymphocytes and occasional plasma cells. In the tonsils the lumens of the crypts are filled with necrotic material, and the sinuses are laden with bacterial emboli, which are surrounded by lymphocytes, plasma cells and monocytes. The lungs, with the exception of those showing terminal bronchopneumonia, contain scattered areas of superficial hemorrhage and pleural exudate; this is laden with erythrocytes and bacteria, but no granulocytes.

Until recently, it was accepted generally that the changes in the bone marrow were in the nature of aplasia which was characterized by the disappearance of the granulocytes and their precursors. Fitz-Hugh and Krumbhaar,[25] Dameshek and Ingall[26] and Baldridge and Needles[27] reported several cases in which the bone marrow showed myeloid hyperplasia, with myeloblasts and myelocytes present in normal or increased numbers. Grossly, the bone marrow shows patchy necrosis and varies in color from red to straw. In both the hyperplastic and the aplastic forms the granulopoietic cells disclose marked retrograde change. This is best demonstrated by fresh smears obtained from the marrow of a rib, the sternum or a tibia, with the method of Isaacs.[28] The change is

25. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of Bone Marrow in Agranulocytic Anginas, Am. J. M. Sc. **183**:104 (Jan.) 1932.

26. Dameshek, W., and Ingall, M.: Agranulocytosis (Malignant Neutropenia), Am. J. M. Sc. **181**:502, 1931.

27. Baldridge, C. W., and Needles, R. J.: Idiopathic Neutropenia, Am. J. M. Sc. **181**:533, 1931.

28. Isaacs, R.: Physiologic Histology of Bone Marrow; Mechanism of Development of Blood Cells and Their Liberation into Peripheral Circulation, Folia haemat. **40**:395, 1930.

first recognized in the cyptoplasmic granules which swell, losing their distinct outline, and are surrounded by vacuoles. At the same time the nucleoli disappear, and the chromatin of the nucleus is broken up into coarse clumps. The nucleus shrinks; the cytoplasm coagulates, and the cell disappears. In the aplastic marrow the reticular structure is prominent and contains a small number of cells, which consist chiefly of large and small lymphocytes and an occasional normoblast and megakaryocyte. Cells of the myelocytic group are uncommon. The hyperplastic marrow is characterized by normal cellulosity; mature neutrophils and eosinophils are absent, and myelocytes and promyelocytes, with their large palely stained nuclei and finely granular cytoplasm are seen in normal numbers (from 20 to 30 per cent). The marrow contains in addition many large mononuclear cells, lymphocytes and normoblasts and large macrophages. Jaffé [29] reported two cases in which erythropoiesis was seen in the most immature stage.

DIAGNOSIS

The diagnosis of granulocytosis with angina is relatively simple. Frequent and early recourse to hematology, with the aid of supravital staining, is of inestimable value, especially in the absence of angina, in which case the patient may complain only of the usual malaise and prostration. In treating the ulcerative lesions in the nose and throat the largyngologist frequently encounters acute leukemia, infectious mononucleosis and Hodgkin's disease. Acute follicular tonsillitis, Vincent's angina and diphtheria, which at times present confusing local lesions in the pharynx, are characterized by the absence of leukopenia. In streptococcic sore throat the number of leukocytes is rarely less than 4,000, and neutrophils constitute approximately 85 per cent of the total number of cells. The utmost care must be used in the elimination of leukopenia resulting from exposure to the roentgen rays (gamma rays) and to drugs such as arsphenamine, amidopyrine, di-nitrophenol, benzene and salicylic acid, all of which contain the common benzene radical. Madison and Squier [15] recently showed, as was previously noted, that amidopyrine, either alone or in combination with the barbiturates, is capable of producing granulopenia in patients as a result of allergic reaction. Leukopenia is similarly found in such systemic states as idiopathic aplastic anemia, aleukemic leukemia and myelophthisic anemia and in typhoid fever, malaria, kala-azar, influenza, glanders, dengue, tuberculosis and fulminating septicemia. In aplastic anemia the infectious manifestations may be similar, but the onset is usually not so abrupt, and the disease runs a subacute chronic course. Both conditions show severe neutropenia.

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29. Jaffé, R. H.: Bone Marrow in Agranulocytosis (Pernicious Leukopenia), Arch. Path. **16**:611 (Nov.) 1933.

ROENTGEN THERAPY

When Friedemann first suggested irradiation of the bone marrow as a method of treatment for agranulocytosis he was under the erroneous impression that small doses of the roentgen rays have a qualitatively different (opposite) action from larger doses—that small doses are "stimulating," while larger doses are "depressant" or destructive. Investigators are now agreed that there is no such thing as a stimulating dose of the roentgen rays in the sense of a dose which acts in a qualitatively different way from a larger dose. The small and the large dose differ quantitatively, but not qualitatively.

Early workers with roentgen therapy for agranulocytosis almost invariably adopted a very small dose (from 30 to 50 roentgens [r]), because they were imbued with the idea that there was danger of exceeding the imaginary quantity of rays at which stimulation ceases and depressant action begins. A recent review of all available reports of cases suggests that doses of from 30 to 50 r are too small, and that a dose of 150 r is more rational. The basis for my choice of 150 r is as follows:

1. When success attended the administration of doses of from 30 to 50 r, a study of the case revealed the fact that the small dose was repeated daily or approximately daily in three, four or five doses, and the desired increase in the granulocyte count did not appear until several such small doses had been administered. Since it is well known that the effects of irradiation are to a marked extent cumulative, it is obvious that a series of daily doses of 30 to 50 r are tantamount to a single dose of somewhat larger size.

2. The literature contains a few instances of the successful employment of single doses of larger size (from 125 to 250 r), and in such cases the desired increase in the granulocytes took place promptly, often within twenty-four hours, whereas the favorable reaction was often delayed five, six or eight days when the repeated small doses were employed.

Indications for Roentgen Therapy in Agranulocytosis.—Until relatively recently, it was generally believed that the bone marrow in agranulocytosis is invariably aplastic. It is now known that a high percentage of patients show normal or more than normal accumulations of progenitors of granulocytes in bone marrow and other leukopoietic tissues,[25] and that in such cases the disturbing factor is not failure of development of blasts but failure of blasts to mature and migrate into the circulating blood. Since one of the most characteristic effects of irradiation is the hastening of maturation of progenitors of blood cells, roentgen therapy is most rational. When bone marrow biopsy is unob-

tainable, I believe that roentgen therapy should be employed on the chance that the case will prove suitable. In cases in which ample studies of the bone marrow have shown progenitors of granulocytes in normal or increased numbers, roentgen therapy is, in the present state of knowledge, strongly indicated. In cases in which microscopic study of bone marrow removed from a rib or the sternum shows a dearth or absence of progenitors of granulocytes, the advisability of roentgen therapy may be questioned, but even in such cases there is an indication for roentgen therapy if the bone marrow is crowded with other cells so as to suggest that the progenitors of the granulocytes are being crowded out. In cases in which biopsy reveals a truly aplastic bone marrow, roentgen therapy is, in my opinion, contraindicated.

Technic of Roentgen Therapy in Agranulocytosis (as Recommended by Dr. Edward Chamberlain of Temple University Hospital).—On the first day 150 r is applied to a wide area over the back of the thorax so as to include the scapulas, the upper ends of the humeri, most of the thoracic spine and most of the ribs. On the second day 150 r is applied to the dorsal aspect of the lumbar region and the lower part of the thorax, the upper margin of the field corresponding with the lower margin of the first day's field of treatment. On the third day 150 r is applied to the front of the thorax, for the ribs and sternum. (The blood count is carefully checked daily, and if a sharp rise in the granulocytes takes place within the first twenty-four hours, omission of the second treatment is suggested, with irradiation of the sternum and ventral ribs on the third day and subsequent irradiation [in doses of 150 r] confined to smaller areas [from 100 to 200 sq. cm.] over selected bones, at the discretion of the roentgenologist and hematologist.) The roentgen therapeutist should select areas for treatment which would permit irradiation of as large a proportion of the total volume of active bone marrow as possible, while avoiding the constitutional reaction that occurs when large volumes of abdominal viscera are included in the field. He must remember that little active bone marrow can be expected in the distal portions of the extremities, while the most active marrow is found in the vertebrae, ribs and sternum, and he must be prepared to abandon his program of roentgen therapy as soon as daily blood counts indicate that the granulocyte count is not registering the desired rise.

SUMMARY

Over any given field of bone marrow a single dose of 150 r is more rational than a series of daily smaller doses.

Whenever possible, the administration of roentgen therapy should be preceded by biopsy of bone marrow, preferably from the sternum or a rib. When this is done, roentgen therapy is indicated in all cases with

hyperplastic bone marrow and is justifiable in certain other cases, but is contraindicated when the marrow is aplastic.

If 150 r has been administered over a fairly large fraction of the active portions of the bone marrow and a sharp rise of the granulocytes is not obtained within seventy-two hours, roentgen therapy should be abandoned.

Other Methods of Therapy.—Transfusions, both in large and small doses, have been used without avail. Pentnucleotide is now considered by many clinicians as one of the best of the newer remedies, but must be given early and often to be of specific value. As has been mentioned, the association with menstruation gives thought as to the administration of the female hormone of the anterior lobe of the pituitary gland. This is a research problem which is now being studied by Konzelmann, who expects to publish his findings and the results of his laboratory experiments shortly.

Recently, organic sulphur has been suggested because of its beneficial effects on bone marrow.

One thing stands out definitely—all coal tar products and aniline dyes should be withheld or withdrawn from the patients until these products are proved definitely to cause no ill effects.

To this lengthy list I shall add one personal suggestion. The thymus is known to have an effect on the formation of blood and plays a definite part in disease of the blood system, which is best demonstrated by the entity of status lymphaticus.

It would perhaps be worth while to try thymic extract in this disease or at least to attempt experimentation along this line. It might add one more stumbling block, but, on the other hand, it might give some help in these frequently hopeless cases.

REPORT OF CASES

CASE 1.—I. H. W., a white man, aged 54, the father of a physician, was admitted to Temple University Hospital at 5:30 p. m. on July 25, 1933. He was a foreman of a mine, working in collieries in Schuylkill County, Pa. Six weeks before, while working at his regular occupation, he complained of severe sore throat accompanied by high fever. Examination showed a swelling in the peritonsillar area. An incision made eight days after the onset elicited little, if any, pus. The temperature remained high, and the patient became delirious. He was treated at this time by his son and local physicians, and the symptoms and condition gradually subsided after five weeks. He was apparently normal and free from all symptoms and, according to his statement, "felt quite well" for one week, when suddenly the former condition, with all the symptoms, pain and fever, with the definite swelling on the left side of the neck, involving all the cervical glands, returned.

Physical examination showed a well developed, well nourished middle-aged man. The head was grossly normal. The pupils responded poorly to light and

were contracted. The ears were normal. The nose showed congested mucous membrane, with some mucopus in each side. The breath was fetid, and examination of the teeth revealed many cavities. The oropharynx was highly inflamed. There was a large indurated swelling over the left tonsillar region, from which a white purulent material was exuding; this was the result of the previous incision. Many small areas of ulceration appeared over the pharyngeal membrane.

The auricular appendage was displaced outward and was tender on pressure. The chest and abdomen were grossly normal. The temperature on admission was 102 F. and gradually rose to 104 F., finally reaching 106 F. before death, which occurred on the third day of hospitalization. The pulse rate ranged from 120 to 160 during his stay; the respiratory rate ranged from 30 to 50 per minute.

During his short stay everything was done for him in line with present knowledge. Nucleotide in ampule doses was immediately given, and combined digitalis and brandy for cardiac stimulation were found necessary. Transfusions were resorted to. Injections of dextrose, roentgen therapy and many other measures were instituted, but in spite of augmented care and treatment he died on the third day in the hospital.

On admission the blood picture was 3,730,000 erythrocytes and 1,600 leukocytes, with 50 lymphocytes. On the second day, in the morning, the red cells had increased to 4,020,000, whereas the leukocytes had decreased to 1,150 and in the afternoon to 1,050, the next day dropping to 650, with 2 neutrophils and 98 lymphocytes.

CASE 2.—Miss S. Y. S., a white woman, aged 50, was admitted to Temple University Hospital on April 10, suffering from (according to the working diagnosis) (1) streptococcic cellulitis, (2) possible Ludwig's angina and (3) agranulocytic angina.

She was a school teacher. While at school on April 6, or four days previous to admission to the hospital, she suffered a severe chill, which lasted for fully forty minutes. She was brought home and put to bed and was seen by Dr. Astley on Friday morning. Dr. Astley stated that her entire throat was highly congested, but no membrane was seen. Her temperature at this time was 101 F. On the patient's lips at the mucocutaneous junction was noticed an area of about from 0.5 to 1 sq. cm., giving the appearance of a contusion of this part, almost as though a hematoma had formed. Another area, which was similar in all respects, was noted at the medial area on the thumb. On Sunday the patient became delirious and difficult to keep in bed. Breathing became costal in type and labored. The amount of mucus in the throat was decidedly increased.

Examination of the throat showed a highly congested pharyngeal mass covered with innumerable shreds of tenacious mucus. The auxiliary lymph nodes on the left side were shotty and easily palpable. The left arm was swollen down to the fingers. The thumb still showed a highly inflamed area. The pulse was irregular, fleeting and weak. The patient was moribund.

The temperature was 104 F., the pulse rate 130 and the respiratory rate 40. The blood count showed 11 Gm. of hemoglobin; red cells numbered 3,490,000 and leukocytes 50.

As the patient was in such a precarious condition, little could be done. She did, however, receive 20 cc. of pentnucleotide intramuscularly and another 20 cc. mixed with 150 cc. of physiologic solution of sodium chloride intravenously, without any reaction. She died at 6:45 p. m. on the day of admission.

DR. JAMES B. COSTEN, St. Louis: Each year the records of agranulocytosis pile up in increasing volume, and it is more and more evident that the actual

number of cases is increasing. This comprehensive review brings the evidence completely up to date with the addition of what may prove to be a most valuable step in the therapy.

The increase in roentgen dosage sounds logical, but I am not in a position to discuss the merits of roentgen therapy. The milder "stimulating doses" were used in each of my cases, as well as transfusion. I think the suggestion of an early biopsy of the bone marrow, to enable one to estimate accurately the granulocyte progenitors, is excellent, since every decision regarding this rapidly fatal disease must be made quickly.

An early sign which has been described in almost all cases seen at onset has been an undermining spot on the anterior pillar, many times incised for a peritonsillar abscess. From the impression gained by the various case reports, I am convinced that this sign is constant. The pathology underlying this phenomenon was originally described by Piette, as a "sudden undermining of normal mucosa with clinical and histologic evidence of the lack of cell reaction of leucocyte accumulation for defense." It seems clear that grayish-white patches represent the stage at which this necrosis breaks through the surface of the mucosa.

The recent work of Madison and Squier and of Kracke emphasizes the importance of the amino derivatives of benzene, notably amidopyrine and a barbital derivative, as bone marrow depressing agents, the studies of Kracke showing that the oxidation products, rather than the original drug, give the depressing effect.

One must recognize the fact that the drug market is flooded with substitutes for all of the well known products. Reliable pharmaceutical laboratories are making efforts to protect the public from such fraud. Little or no control is exercised over the purchase of these drugs, and with or without a doctor's prescription the patient many obtain unlimited amounts. He has every chance of obtaining a dangerous product. In addition to personal susceptibility it seems that this situation may be a factor in the alarming increase in the production of cases of malignant neutropenia.

DR. CLAUDE L. LARUE, Shreveport, La.: While more is yet to be learned on the subject of agranulocytosis, one may now, after ten or twelve years of interesting and intensive study, venture the following postulates: (1) that agranulocytosis exists as a definite, clearcut, disease entity; (2) that leukopenias exist with accompanying serious clinical manifestations, secondary to the use of agents depressive to bone marrow function, the benzene ring group of drugs being the outstanding offenders; (3) that there are clearcut diagnostic laboratory methods which make differentiation positive; (4) that the more promptly diagnosis is made and treatment begun the better the prognosis, this being true to a far greater degree than in the case of most other diseases one treats, and (5) that regardless of unproved etiology, treatment has been greatly improved during the past three or four years.

Most important is its early recognition, and this is a matter of making white cell and differential blood counts early and repeatedly.

I am not sure of being in complete accord with Dr. Ridpath's views as to treatment, especially in the fulminating cases. If I understand him correctly, he considers rather intensive irradiation of the long bones the treatment par excellence. Even assuming the possibility of permission for biopsy and the correct differential determination of hyperplastic or aplastic bone marrow, if he is correct in believing that the small and large doses of roentgen rays do not differ in results except quantitatively, and since certain doses of irradiation are without doubt followed by neutropenia, the logic of roentgen treatment seems open to question. On the other hand, both blood transfusion and pentnucleotide, likewise adenine sulphate, give good results, apparently regardless of the condition of the bone marrow. Trans-

fusion must be frequent and in large amount. From the report of the nucleotide committee of the Harvard Medical School by Dr. Jackson, one cannot but believe in the efficacy of pentnucleotide. It was used in sixty-nine cases, reported by forty physicians over twelve states, with recovery in 74 per cent. Regardless of the fact that such statistics may be misleading unless the patients treated are classified as to the severity of their condition, that report is most encouraging.

In my own opinion, the following therapeutic measures are the most effective ones in the order named: pentnucleotide, transfusion and irradiation.

If laryngologists and physicians who usually see the patients first will insist on early and repeated studies of the blood, and if methods of treatment continue their pace of improvement, agranulocytosis will, in the second decade of its recognition, become a disease showing practically 100 per cent recoveries rather than 100 per cent fatalities.

Dr. John J. Shea, Memphis, Tenn.: Today we are seeing a greater number of cases of "agranulocytic angina," either because the disease is more frequent or because the average laryngologist is better trained. There are two varieties: one, which ends fatally and is most frequently seen in middle-aged women, and of which we have had three cases; the second variety is a symptom complex and of this type we have had four cases. The etiology of the disease is not definitely known. Various observers have isolated the following organisms from lesions of the throat: Bacillus pyocyaneus, hemolytic streptococci, nonhemolytic streptococci, staphylococci and Vincent's bacteria. The toxin producing this malady is capable of paralyzing the hematopoietic system, especially the bone marrow, where the myeloblasts are producing granular units. The usual initial lesion in the pharynx consists of a necrotic ulcer on one of the tonsillar pillars, accompanied by a localized swelling of the region suggestive of a peritonsillar abscess.

The laryngologist has an opportunity to study the relationship of the anginas and the hematopoietic response in the following diseases: agranulocytic angina, acute infectious mononucleosis, Vincent's angina with a lymphoid leukocytosis and acute lymphadenosis.

The anginas are capable of producing four types of changes in the blood: (*a*) polymorphonuclear leukocytosis as seen in follicular tonsillitis and septic conditions of the throat; (*b*) mononuclear leukocytosis such as occurs in infectious mononucleosis; (*c*) leukopenia with a decrease of granulocytes—agranulocytic angina; (*d*) leukocytosis with a relative hypergranulocytosis, as seen in the patients suffering from a generalized Vincent's infection.

The pathologic study of the tonsil removed in a fatal case failed to exhibit any characteristic changes. Atrophy of the lymphoid elements was the most pronounced change.

The notoriety given to amidopyrine as a cause of this disease is an injustice to this valuable drug. My experience with pentnucleotide has been too limited to justify an expression of its value.

Dr. William H. Gordon, Detroit: Up to the present time not many cases have been seen which could be attributed to the amidopyrine group. I know of only one case which might be attributed to it, and that is not an absolute fact.

In a series of over fifty-seven cases blood counts were performed three and four times a day. Every form of treatment which has been listed was tried and I observed four patients in whom the condition developed in the hospital while under medical observation. For weeks not one of them had had any of the drug series. All of them were under observation for some chronic condition, such as disease of the heart, kidney or gallbladder. These cases were most interesting from the standpoint of studies of the blood. Within four days after a rise of temperature

and a severe sore throat developed there were absolutely no polymorphonuclears in the blood stream. The polymorphonuclear white cell count began going down with the beginning of the sore throat, or a short time before. One patient had a normal count when she entered the hospital. A sore throat developed on the second day, and the white cell count was 3,500, with 10 per cent polymorphonuclears. In studying these cells, we found that the last type of polymorphonuclear cell found in the blood stream was the terminal stage or the multinucleated white blood cell. The first cell that occurred in the blood stream of this patient was the young cell from the bone marrow. My belief at that time was that the condition was probably not a peripheral leukotoxic disease but one which affected the bone marrow primarily. In three similar cases the same alterations have been observed.

From a review of reports up to the last two months it appears that 50 per cent of the cases present icterus. This is not correct. The physicians who report this have not studied the literature. Doan and Kracke reported that they have not seen any patients with it. In our series of over fifty cases there were five instances of icterus, a ratio corresponding to that noted in the literature. About 5 or 6 per cent of the patients have it. In the cases in which icterus was present, it usually occurred following blood transfusions, which suggested that the icterus was the result of the destruction of the fresh blood given to the body instead of being a symptom of the condition.

Roentgenotherapy was tried without obtaining results. Blood transfusion gave the best results. For that reason, in Detroit blood transfusions in small doses have been advocated.

Dr. Henry N. Harkins, Chicago: All those who preceded me in the discussion have played an important part in elucidating various factors concerning this disease. Dr. Shea has shown that the granulopenias could be divided into two classes. Dr. Gordon is one of the first men in this country to suggest that this is a disease originating in the bone marrow. Dr. LaRue is one of the first otolaryngologists to discuss this disease and show its importance in otolaryngology. Dr. Costen was the second man in this country to show that the amino derivatives of benzene are possibly of importance in the etiology of agranulocytic angina.

The condition has an important bearing on the entire cellular theory of immunity. Kracke and others have shown that the secondary angina occurs after the onset of the agranulocytic condition, and Dr. Ridpath demonstrated this relationship very well in his cases.

The secondary anginal or ulcerative changes are a result of lowered resistance in places where trauma and bacterial flora will cause injury and secondary invasion. This condition occurs especially around the tonsils, as has been shown by Dr. Ridpath. But it may also occur in other parts of the body. Patients have come to general surgeons complaining only of an ulcer around the anus, but the blood count revealed the typical condition. One of my patients when seen had a lowered white cell count, but no ulcers. Three days later, opposite some rough fillings in his teeth ulcers developed, and two days later he died with severe sepsis, abscesses in the lungs and suppuration in the mediastinum.

Another patient with severe granulopenia had counts made on blood from various fingers successively. After these counts red streaks developed up each finger, following the course of the lymphatics and illustrating the lowered resistance. This condition is one of many disturbances, such as pernicious anemia, syphilis and disseminated sclerosis, the local manifestations of which may cause the patient to consult various specialists.

Dr. Robert F. Ridpath, Philadelphia: It is quite plausible that one physician would have favorable results with blood transfusions, while others would obtain

no benefit. It then becomes a personal equation whether blood transfusions should or should not be given.

Essentially the question of blood transfusions must be considered from the reports of repeated examinations of the blood, and we must consider not only the number of white and red cells but the character of these elements as well as the general character and condition of the blood stream itself. It is only by this constant supervision and repeated examinations that we are enabled to say that a patient should have a blood transfusion, or that another one would be made worse by a transfusion.

Again treatment by the roentgenologist must essentially be considered under the same head, and the dosages, as well as the irradiated territories, must be very carefully considered in each case.

In my paper I have presented the consensus of Dr. Chamberlain and other roentgenologists as to the method, the territory and the dosages which would be advantageous in this particular disease. We may differ in some of our therapeutic methods, but we are all trying to find what is the best treatment for the unfortunate patient with this disease.

FURTHER RESEARCH ON EXPERIMENTAL AND CLINICAL SINUSITIS

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SYNOPSIS OF EXPERIMENTS

During 1933 and 1934 our work was directed along several lines, using the cat's frontal sinus, in which chronic inflammation closely resembling human types of reaction had been produced by inoculation with human hemolytic streptococci. On completion of each experiment the animal was vital-stained with 1 per cent trypan blue, and the tissues, fixed in situ with formaldehyde-Zenker fluid, were counterstained with hematoxylin and eosin-azur. The technic followed, including the staining of human tissues with eosin-azur, was that used and reported in all the previous research of this series (1930 to 1933).

The procedure was as follows: Each of a series of young cats of the same litter having unilateral chronic (of six weeks' duration) frontal sinusitis (1) was inoculated subcutaneously with 1 per cent peptone, (2) received from 1 to 2 cc. of 1 per cent peptone, injected into the sinus cavity by puncture with a needle or was given an intramuscular injection of 2 cc. of fresh blood from its own femoral vein. Control animals were observed. These procedures, 1 and 2 using peptone as the foreign protein and (3) using the animals' own blood (autohemotherapy), produced evidences of acute exacerbation, infiltration with round cells and perivascular accumulation of histiocytes in the chronically inflamed membranes. Peptone injected subcutaneously seemed to cause the greatest amount of this reparative activity. There was no apparent change from the normal in the uninfected sinuses. Control animals showed no increase of infiltration with round cells or with histiocytes, plasma cells and polymorphonuclears being most frequent in the edematous membrane of the ordinary chronic type of reaction. In a later series typhoid vaccine was injected into the chronically inflamed sinus; there was much epithelial loss, with marked infiltration of the plasma cell layer of the stroma by numerous polymorphonuclears.

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Attempts to demonstrate lymphatic channels of the sinus mucoperiosteum by the use of vital-staining mediums were made as follows: 1. For the study of normal sinuses liquid india ink was placed outside the exposed upper surface of the lining of the sinus after the bony roof had been chipped away or was injected into the cavity. 2. For the study of normal and of infected sinuses a solidifying 1 per cent agar emulsion of 0.25 or of 1 per cent trypan blue was injected into the sinus lumen.

India ink failed to show definite black channels in the submucosa or along the bony walls but caused diffuse blackening of the mucosal surface. Sublingual and deep cervical glands were stained black, but this may have been from the turbinals.

The agar emulsion of 0.25 per cent trypan blue was injected into both frontal sinuses of animals with the right sinus infected for three weeks and the left sinus normal, and the membranes were secured and fixed after seventy-two hours. Much acute edema was present in the normal membrane, especially toward the ostium. Severe chronic edema and visible capillary dilatation, resembling those seen in infected human membranes as removed, were observed in the infected membrane. A deeper surface stain occurred with the agar emulsion of 1 per cent trypan blue. In two animals, noticeable blue channels, possibly lymphatic, were seen passing forward toward the ostium of the sinus, both on the side showing acute and on that showing chronic inflammation, as viewed by microscopic dissection. These channels were not blood vessels and were apparently choked with histiocytes and polymorphonuclears. No lymphatic channels were visible by staining with trypan blue on the bony cerebral aspect, roof or floor of the sinus cavity or on the corresponding periosteal surface of the submucosa. Sufficient time had not, apparently, elapsed for the absorption of trypan blue into the deep cervical glands, though the turbinals were deeply stained.

A total resection of the right cervical sympathetic nerve was performed on cats with bilateral chronic sinusitis. Marked acute edema, congestion and infiltration with round cells took place immediately, in marked contrast to the quiescent, relatively thin membrane full of plasma cells present on the side not sympathectomized.

Various antiseptic, astringent and stimulant solutions were used in the chronically infected sinuses of cats, causing the following changes in membranes which were similar to chronic inflammations in man: 1. Merthiolate, 1 : 1,000, caused severe acute irritation with some recent epithelial loss and invasion by polymorphonuclears; there was no apparent exacerbation toward healing. 2. Alcohol, 95 per cent, exerted a caustic and dehydrating action on the superficial layers of epithelium,

with a loss of cilia and marked subepithelial hemorrhage. 3. An emulsion of oxyquinoline sulphate, 1 per cent, and scarlet red, 1 per cent, markedly stimulated reparative effects, with infiltration of histiocytes and round cells and migration of polymorphonuclears. 4. Mercurochrome, 1 per cent, produced a picture consisting of numerous goblet cells, with a rather marked epithelial loss, migrating polymorphonuclears and patches of recent invasion by round cells and histiocytes. 5. Chloramine, 1:3,000, caused a mild acute exacerbation of the chronic destructive process. 6. Metaphen, 1:5,000, caused fairly mild acute polymorphonuclear and lymphocytic infiltration into severely chronic inflammation. 7. Trinitrophenol, 0.5 per cent, followed immediately by calcium gluconate, 0.5 per cent, thus precipitating the calcium salt of trinitrophenol on the membrane, caused a severe acute exacerbation with marked polymorphonuclear infiltration and diapedesis from capillaries.

A number of human patients with bilateral frontal sinusitis received a single powerful unilateral therapeutic irradiation with roentgen rays according to the method described last year. A clinical examination two months later disclosed a recurrence of the nasal discharge and obstructive symptoms in every case, requiring other methods of treatment. Since a complete report on the tissues of such patients was made last year, none were operated on. It seems evident from this series that irradiation is no guarantee against recurrence, though it seems to promote some degree of fibrosis in membranes presenting simple infiltration with round cells.

Six patients with bilateral sinusitis received diathermic treatments over one antrum twice weekly for from one month to six weeks. Four other patients dropped out after a few treatments, claiming that they obtained relief after an initial stage of congestion. Of the six patients, four were much improved clinically; the fifth was relieved of arthritic pain, and the sixth was freed from obstructive turbinal hyperplasia, while the antral transillumination was improved. Three of the patients who showed improvement were operated on to secure membranes thus treated. These membranes showed, in addition to the usual marked subepithelial layer of plasma cells, a considerable degree of hyperemia and many histiocytes and fibroblasts, evidently resulting from a stimulated process of active fibrous repair.

RECAPITULATION

Injection of foreign protein (peptone, typhoid vaccine or autogenous blood) intramuscularly or into the sinus cavity produces acute exacerbational changes and pericapillary infiltration with round cells and histiocytes similar to the reparative changes aroused by autogenous vaccines.

The lymphatic channels in the sinus submucosa seem to converge toward the normal ostium and to become more or less clogged during

inflammation, apparently by histiocytes and polymorphonuclears, thus giving rise to local edema and mechanical obstruction to drainage of the sinus. These observations require further study by more delicate microscopic and vital-staining methods.

Unilateral cervical sympathectomy performed on cats with bilateral chronic sinusitis brought about active and severe reparative congestion, edema and round cell infiltration in the sinus on that side; the sinus on the other side remained quiescent, showing predominant plasma cell infiltration and no tendency toward repair.

Several powerful antiseptic solutions occasionally used to irrigate the healing antrum after operation and other wounds (merthiolate, 1:1,000, chloramine, 1:3,000, trinitrophenol, 0.5 per cent, followed immediately by calcium gluconate, 0.5 per cent, and alcohol, 95 per cent) produced further losses of epithelium and invasion by polymorphonuclears, and apparently delayed the healing process. Mercurochrome, 1 per cent, metaphen, 1:5,000, and oxyquinoline sulphate, 0.5 per cent, emulsified with scarlet red, 0.5 per cent, seemed to promote infiltration of round cells and histiocytes, to a limited extent, without, however, improving the tendencies toward repair of the mucosal surface.

Our opinion expressed last year, that the therapeutic use of roentgen rays may produce some fibrosis following the destruction of round cells but that no healing of suppurative changes in the submucosa can thus be made to take place, was borne out by the occurrence of exacerbations of varying severity in all of ten patients who had received irradiation and were called back for examination and treatment two months later.

Diathermy applied twice weekly for one month on one side in numerous cases of bilateral maxillary sinusitis produced a rapid clinical amelioration in nearly all; the operative removal of tissues disclosed much recent hyperemia with many histiocytes and some fibrous repair, evidently stimulated by the local and enforced elevation of temperature.

Topics requiring further and detailed study, with eventual clinical application of the results obtained, include: lymphatic obstruction to sinus drainage during infection, local reparative effects of systemic agents acting on the sympathetic system: (acetylcholine, pilocarpine, epinephrine, ephedrine) and attempts to break up or metamorphose infiltration of plasma cells through physical or biochemical agencies.

DETAILS OF EXPERIMENTAL STUDIES

The experimental work was carried out with the technical assistance of Dr. Lyle M. Bain and Mr. Wallace Shearer. The clinical cases were managed by Dr. Victor Adix, resident in otolaryngology. The roentgen treatments were given under the direction of Dr. Ivan M. Wooley, and diathermy was administered by Dr. Arthur Jones.

Use of Foreign Protein.—The right frontal sinus of young cats from the same litter was inoculated with hemolytic streptococci from the human upper respiratory tract, and after six weeks, a period demonstrated by past experiments as sufficient to produce changes simulating those of chronic human sinusitis, various substances were administered:

Cat 501.—Two cubic centimeters of peptone 1 per cent was injected into the infected right sinus cavity. Seventy-two hours later three subcutaneous injections of trypan blue, 1 per cent, were given for vital staining; the animal was killed, and routine fixation of the upper half of the skull in formaldehyde-Zenker fluid, followed by hardening in alcohol, and dissection in toto were carried out as in previous experiments. The right membrane was slightly thicker than the left and was adherent to the bony wall. Microscopic observation showed that the cilia were retained; there was marked subepithelial edema with numerous plasma cells, but numerous pericapillary round cells and histiocytes were found, indicating an acute exacerbation as a result of the injection of peptone. The left membrane (uninfected) was normal except for an unusual number of goblet cells; there were more than the normal number of histiocytes about the small blood vessels.

Cat 502.—This animal received a subcutaneous injection of 2 cc. of 1 per cent peptone; otherwise the same procedures were followed, and the observations were practically the same, as for cat 501.

Cat 503.—Two cubic centimeters of the cat's whole blood was withdrawn from the femoral vein and immediately reinjected intramuscularly. The gross observations were the same as for cats 501 and 502; the infected sinus was rather small, and the dissection was difficult. Microscopically the epithelium contained many goblet cells; there were occasional drifts of plasma cells in areas of marked edema, in which a few histiocytes were present about the small vessels. The left membrane was normal. This cat showed less marked, but evident, reparative effects as a result of autohemotherapy.

Cat 504.—The same procedure was followed as for cat 503. There were slightly more marked pericapillary accumulations of round cells and histiocytes in the infected sinus, but no polymorphonuclears.

Cat 505.—An animal from the same litter, observed as a control, showed only the usual accumulation of plasma cells in an edematous membrane, with no evidence of recent congestion or accumulation of histiocytes in the infected or in the normal membrane.

Study of Lymphatics with India Ink.—Cat 506.—Both frontal sinuses were exposed by carefully chipping off the bony roof and exposing the membrane. On the right side the membrane was opened; on the left it was kept intact. Five cubic centimeters of india ink diluted with physiologic solution of sodium chloride was placed on each membrane, and the external skin and pericranium were sutured. The membranes were fixed in situ after seventy-two hours. No definite channels were visible either on the bone or toward the ostium, but deposits of ink, possibly from blackened turbinals, were found under the tongue and in the superior cervical glands.

Study of Lymphatics with Radiopaque Oil and Trypan Blue.—In a later series, a 1 per cent emulsion of agar with trypan blue or with radiopaque oil was injected into the sinus cavities of animals in which the right sinus had been infected three weeks before and the left was normal. This emulsion was permitted to act for seventy-two hours, producing an acute inflammation of the normal membrane and

allowing a gradual infiltration of the vital-staining agent into the epithelium and tissue spaces, after which the usual fixation and dissection were performed.

CAT 520.—Radiopaque oil was used. This animal had no right frontal sinus, and the injections reached the right orbit. A slight thickening of the left membrane was noted but no definite lymph channels.

CATS 518 and 519.—These animals received trypan blue, 0.25 and 1 per cent, respectively. Both showed acute edema of the uninfected membrane, especially forward toward the ostium. A deeper surface stain occurred with the 1 per cent trypan blue. Severe chronic edema and capillary dilatation were visible on the infected side; the membrane grossly resembled edematous human tissue. Both animals showed a few distinct streaks of blue passing forward near the ostium; these streaks were not blood vessels and were apparently choked with histiocytes and polymorphonuclears. The bony walls of the cavities showed no blue streaking, and the surface of the membrane facing the bone disclosed no streaks or channels on the upper, posterior or lower surface. The edema was most marked toward the ostium in both the acutely (uninfected) and the chronically (infected) membrane. There was dark staining of the turbinals, but no gross evidence of blue dye in the deep glands; the latter were not studied microscopically.

Effects of Sympathectomy.—CATS 510 and 511.—In each animal both frontal sinuses were infected for six weeks; the right cervical sympathetic nerve was sectioned and tissues were secured seventy-two hours later. Destruction of the sympathetic nerve below the superior cervical ganglion was proved by dissection. Grossly the right membrane was thickened and edematous, with injected blood vessels; the left membrane showed a slight thickening and was apparently healing. Microscopic observation of the membrane on the sympathectomized side showed lymphocytes, plasma cells and polymorphonuclears scattered throughout, with beginnings of cystic formation in several places; a rather severe chronic infection with recent mild exacerbation and acute edema and thickening of the membrane. On the opposite side the membrane was only slightly thicker than normal, and there were evidences of healing of the previous infection.

Results of Local Application of Antiseptic Solutions.—CAT 512.—This animal had a bilateral infection with Streptococcus viridans for eight weeks. Oxyquinoline sulphate, 1 per cent and scarlet red, 1 per cent, in aqueous emulsion was injected into the right sinus. Tissues were recovered and fixed after seventy-two hours. The membrane was thick and much injected. Microscopically the mucosa was greatly thickened, being filled with lymphocytes, plasma cells and some histiocytes. The epithelium was much injured and destroyed in patches. Polymorphonuclears were numerous near the surface, some migrating through the epithelium; the sinus cavity contained masses of them. The tunica propria was edematous and congested and contained numerous plasma cells. The total picture was that of a chronically infected membrane with an acute exacerbation, the latter being apparently due to the injection of oxyquinoline sulphate and scarlet red.

The left sinus of this cat was filled with a 1 per cent aqueous solution of mercurochrome. The entire membrane presented the usual gross thickening of chronic infection. Microscopically a part of the membrane gave the picture of mild chronic inflammation, with thickened mucosa filled with plasma cells, lymphocytes and some polymorphonuclears. The epithelium over this area was thickened, showing numerous goblet cells and intact cilia. On the opposite side of the sinus, however, the epithelium had been destroyed, leaving only basal cells and no goblet cells or cilia. In patches the epithelium was destroyed. The tunica propria of

this part of the sinus showed acute reparative inflammation, with numerous polymorphonuclears passing through the remnant of epithelium; some histiocytes and numerous plasma cells were present.

CAT 513.—This animal had been infected bilaterally for six weeks with hemolytic streptococci. Ninety-five per cent alcohol was injected into the right sinus and tissues were secured and fixed in situ after seventy-two hours. Grossly the membrane was much thickened and reddened. Microscopically the usual picture of chronic infection was present, with numerous plasma and other cells. The epithelium was injured throughout; the cilia were largely destroyed; in some parts only the basal layer of cells remained. Elsewhere the epithelium was absent, and beneath these regions there was marked hemorrhage. The total picture was that of a chronically inflamed membrane in which a severe exacerbation had been caused by the recent local use of alcohol; there was no indication of recent infectious activity or of any stimulation toward repair.

A 1:1,000 aqueous solution of merthiolate was injected into the left sinus of this cat. The membrane of the sinus was greatly thickened. Microscopically the mucosa was extremely thickened, being filled, like that on the right side, with polymorphonuclears and plasma and other cells. The epithelium was almost totally destroyed; that which remained was filled with migrating leukocytes. The tunica propria was thicker than in any other animal of the series and contained numerous plasma cells, macrophages and, near the epithelial surface, many polymorphonuclears. Some fibrosis was evident in the deeper part of the tunica propria. The total picture was that of a chronic, severe infection of the sinus membrane on which had been superimposed a severe and destructive inflammatory flare-up, apparently caused by the solution of merthiolate.

CAT 514.—This animal had had a bilateral streptococcic infection for six weeks. On the right side no sinus was found on dissection, the 1:5,000 solution of metaphen used having entered the orbit. The left sinus, into which a 1:3,000 aqueous solution of chloramine had been injected, showed the usual picture of chronic infection, with a mild acute exacerbation from the chemical used.

CAT 515.—Cat 515 had been infected bilaterally with Str. viridans for nine weeks. A 1:5,000 aqueous solution of metaphen was injected into the right sinus. This cat and cats 516 and 517 showed a more marked response to the original infection than did most of the animals reported on previously in this series. The membrane was notably thickened on removal, and the microscopic sections showed a mild chronic type of infection, with a recent exacerbation indicated by numerous polymorphonuclears. The epithelium was destroyed in patches.

The left frontal sinus, into which a 1:1,000 aqueous solution of merthiolate had been injected, showed marked thickening on gross observation. Microscopically the stroma was very thick, with numerous plasma cells throughout. Near the surface were many polymorphonuclears, of which large numbers were migrating through the destroyed epithelium. All the blood vessels were greatly dilated, with some extravasation. As in cat 513, the merthiolate had apparently produced definite irritation and destruction.

CAT 516.—This animal, which was infected as was cat 515, was found to have no right frontal sinus; this fact made the injection of a 0.25 per cent solution of silver nitrate act merely as a vital-staining medium for the right orbital tissues. The left sinus, which was filled with typhoid vaccine, showed the usual gross and microscopic changes due to chronic infection. The epithelium was much injured, with leukocytic migration going on. The outer layers of the tunica propria were

crowded with polymorphonuclears. This showed a definite acute reparative exacerbation on top of the old process.

CAT 517.—This animal, which was infected as were cats 515 and 516, received an injection of trinitrophenol, 0.5 per cent, followed by an injection through the same needle of calcium gluconate, 0.5 per cent, simulating the treatment of osteomyelitis wounds with trinitrophenol and calcium carbonate advocated by Stewart. The membrane, greatly thickened, showed on microscopic observation severe epithelial damage with patches of denudation. Numerous plasma cells and some polymorphonuclears were found subepithelially. Leukocytic migration was frequent, and the lumen was filled with polymorphonuclears. The tunica propria was greatly thickened and edematous. The total picture was that of an old, chronically inflamed membrane with recent, in some places very severe, exacerbation.

The left sinus was filled with a 1 per cent solution of peptone. The recovered membrane was relatively thin. Histologically, the epithelium was tall, with numerous goblet cells. The cilia were partly destroyed, and some migration of leukocytes was taking place through the epithelium. The tunica propria was thin but contained some plasma cells. Some residual infection was evident, but at nine weeks healing had gone further than in other animals of the series. The peptone did not cause a flare-up but appeared rather to have helped the healing process. This membrane showed the nearest approach to a normal appearance of any of the experimentally infected sinuses.

RESULTS OF DIATHERMY ON HUMAN MEMBRANES

Three of six patients with bilateral maxillary sinusitis treated from eight to eleven times by diathermy over the left sinus only were operated on from four to five weeks after the end of the course of treatments. Grossly, the treated membrane in one case was still much thickened and more hyperemic than in the average case of polypi; in another case, the irradiated membrane had become definitely thin and good transillumination had returned before operation. The untreated membranes presented the usual picture, namely, masses of plasma cells, cysts and marked edema. After treatment with diathermy, even in the thick membranes, and in spite of marked subepithelial infiltration of plasma cells, a large number of histiocytes could be located near the capillaries, which were distinctly dilated. In the thin membranes which had been treated with diathermy there were numerous histiocytes and fibroblasts, fairly marked congestion without edema, and a number of eosinophils. Evidently the continuing hyperemia from this form of diathermic therapy assists in bringing in cells which are concerned with repair by fibrosis.

PRENATAL MEDICATION AS A POSSIBLE ETIOLOGIC FACTOR OF DEAFNESS IN THE NEW-BORN

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The study of deafness and its etiology has received more attention in the last decade than in any other period of history. Much light has been thrown on the subject, many new theories have been advanced and many old ones abandoned. It is generally estimated that there are now more than 10,000,000 deaf persons in the United States, 3,000,000 of whom are children. These statistics have doubtless been a stimulus to the otologist in studying the various phases of deafness. The report of the committee on statistical studies of the children in public schools for the deaf,[1] made to the National Research Council, states that of 5,348 deaf children examined by the committee, 3,334, or 62.15 per cent, were classified as congenitally deaf. It also states that congenital syphilis plays only a small part as a causative factor of deafness. This finding is in line with the assertions of McCarty,[2] who, after seventeen years of close study of the syphilitic child, concluded that there is no proof of an abnormal tendency to deafness in congenital syphilis. In his functional testing of more than 1,000 subjects he found normal hearing in practically all who had not had otitis media. Such statements as these seem to demand that science turn to a profound study of the etiology of that type of deafness which has come under the broad classification of congenital deafness.

The phase of the subject of deafness in the new-born which suggests the possibility of certain drugs which have been administered to the pregnant mother passing through the placental circulation and damaging the ear of the fetus has been virtually ignored by the otologist.

PREDILECTION SHOWN BY CERTAIN DRUGS FOR THE AUDITORY NERVE

All modern textbooks on otology refer to the fact that certain drugs have a selective action for the auditory apparatus and can cause nerve

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Read before the Section of Laryngology, Otology and Rhinology at the Eighty-Fifth Session of the American Medical Association, Cleveland, June 14, 1934.

1. Shambaugh, G. E.: Hayden, D. B.: Hagens, E. W., and Watkins, R. W.: Statistical Studies of the Children in Public Schools for the Deaf, Arch. Otolaryng. **12**:190 (Aug.) 1930.

2. McCarty, Virgil W.: Otological Observations in the Congenital Syphilitic Child, Tr. Am. Laryng., Rhin. & Otol. Soc., 1932, p. 479.

deafness. Politzer [3] stated that the action of drugs circulating in the blood affects the auditory nerve more often than any other of the nerves of special sense. It is known that such drugs as quinine, the salicylates and alcohol can have a permanent influence on the eighth nerve. It is also known that quinine has a predilection for the auditory nerve and, as Politzer [3] stated, "subjective noises and deafness take place in from one to two hours after its ingestion." He further asserted: "The predilection which quinine has for the auditory nerve causes the most severe pathological changes leading to a deafness of a varying degree and even to a permanent loss of hearing function in one or both ears."

The general use of certain drugs has shown that many persons have curious idiosyncrasies in regard to them. For example, many persons after taking small doses of quinine show pronounced symptoms, such as cutaneous eruptions, a rise in temperature, marked tinnitus and deafness. In some persons these symptoms develop from as small a dose as 5 grains (0.3 Gm.). My mother has a definite idiosyncrasy for quinine. Following the administration of 3 grains (0.19 Gm.) of this drug she experiences marked erythema, a rise in temperature, noise in the ear and deafness. That neither her parents nor her three children have ever shown any idiosyncrasy for this drug seems to indicate that the presence or absence of an idiosyncrasy for quinine in the mother need have no significance, so far as the offspring is concerned. In my review of the literature, however, I found reports of 18 cases of fetal death attributed to the toxic effect of quinine administered during labor, and in them were repeated references to the part that idiosyncrasy for this drug seemed to play, and frequent mention was made of tinnitus, deafness and urticaria occurring in the mother following its use.

Numerous writers have reported their observations of the effect which various drugs have on the ear. Wittmaack [4] noted degeneration atrophy of the ganglion cells and nerve fibers in the basal coil of the cochlea as a result of the administration of quinine and observed similar changes in the lamina spiralis. He concluded that deafness is permanent when the basal coil of the cochlea is injured. Beck [5] and others reported degenerative changes in the ganglion cells of the cochlea resulting from use of the salicylates. Haike [6] reported that the permanent deafness which sometimes occurs as a result of the administration of salicylates is due to the irreparable injury to, and destruction of, the spiral ganglion

3. Politzer, A.: A Textbook of Diseases of the Ear, Philadelphia, Lea & Febiger, 1926, p. 647.

4. Wittmaack, K.: Ztschr. f. Ohrenh. **51**:161, 1905-1906.

5. Beck, K.: Experimentelle Untersuchungen über den Einfluss von Bakterientoxinen und Giften auf das Gehörorgan, Ztschr. f. Ohrenh. **68**:128, 1913.

6. Haike, H.: Experimentelle Untersuchungen zur Kenntnis der Wirkung des Natrium salicylicum auf das Gehörorgan, Arch. f. Ohrenh. **63**:72, 1904.

cells. Lazinier [7] stated that quinine is the chief drug that causes aural symptoms and that second in importance are the salicylates. He reported 2 cases of deafness and tinnitus due to the use of sodium salicylate in which neither patient had had any previous disease of the ear, and he noted that permanent deafness may result from the use of quinine and salicylates by persons who are especially suseeptible to the toxic action of these drugs. It seems to be the consensus of both the ophthalmologist and the otologist that the deafness and amblyopia caused by quinine and the salicylates are due to the contraction of the blood vessels of the internal ear and the retina and that the resulting ischemia, lack of nutrition and anoxemia may cause degeneration of the ganglion spiralis, the organ of Corti and the retina. Klugkist [8] stated that deafness caused by alcohol is not frequent and that it is due to injury of the hair cells of the organ of Corti, the injury being most marked at the basal turn of the cochlea.

PERMEABILITY OF PLACENTA TO DRUGS

It seems strange that the otologist has virtually ignored the fact that drugs which produce nerve deafness when administered to the pregnant woman pass on through the placenta and can be found in relatively large amounts in the fetal circulation, and also that the fetal tissues seem to react to them in the same manner as do the tissues of the mother. My purpose in this article is to arouse the interest of the otologist in the possibility that these drugs may pass from the maternal circulation into the fetal circulation and injure the eighth nerve and the ganglion cells of the internal ear of the unborn child. That the placenta is permeable to drugs has long been recognized. The obstetrician has for many years accepted this fact, and since it has become recognized that quinine, when administered to the mother, may be toxic to the fetus, much research work has been done on the subject. It is interesting to note that Dilling and Gemmell [9] stated that on examination of the urine of 17 babies whose mothers had been given quinine in the induction of labor, they found the drug in the urine of 16. They also stated that quinine is found in the urine of the fetus six to twelve hours after the last dose is administered to the mother, and that a concentration of quinine which may be toxic to the fetal tissues may persist in

7. Lazinier, J. E. J.: Contribution à l'étude des surdités toxiques, Thèsis de Paris, 1899.

8. Klugkist, H.: Ueber die Alkohol-Vergiftung des Gehörorgans, Thesis, Göttingen University, 1928.

9. Dilling, W. J., and Gemmell, A. A.: A Preliminary Investigation of Foetal Deaths Following Quinine Induction, J. Obst. & Gynaec. Brit. Emp. **36**:353, 1929; Further Investigations of the Death of the Child Following Induction of Quinine, ibid. **37**:528, 1930.

the fetus many hours after the wave of secretion in the maternal urine has subsided, owing probably to the slow return of the drug from the fetus to the mother or to inability of the fetal kidneys to excrete the drug in such a concentration.

Torland [10] stated that two hours after 10 grains (0.64 Gm.) of quinine sulphate was given to a mother, ringing in her ears, deafness and urticaria developed. Shortly after the quinine was administered she felt strong movements of the baby, but several hours later was delivered spontaneously of a stillborn child. Autopsy performed on the baby showed acute tubular and glomerular nephritis. Torland concluded:

> It is known that quinine is a protoplasmic poison, attacking preferably the cell protoplasm, and it is not improbable that this protoplasmic poison, circulating in the maternal blood and entering into the fetal circulation, might cause such extensive injury to the fine fetal cells that death would result.

King [11] reported a fetal death resulting from quinine given to the mother and stated that he obtained from the brain of the fetus appreciable quantities of quinine and also found it in the urine. Kirby-Smith [12] cited a case of urticaria due to quinine in a new-born infant that he attributed to quinine administered to the mother for the purpose of inducing labor. These reports seemingly indicate that the fetus in utero in some cases suffers from the toxic effect of quinine, a known protoplasmic poison.

Porak [13] reported finding sodium salicylate in the urine of infants in cases in which the drug had been given to the mothers thirty minutes before delivery. He stated that the concentration was greater several hours after birth than at birth and that it was found in the urine for as long as three days.

In his experiments on women in labor Nicloux [14] gave alcohol in milk an hour before delivery of the child. This drug was demonstrated in the blood of the umbilical cord in practically the same concentration as in the maternal blood. Nicloux asserted that the placenta acts as a dialyzer of drugs present in the maternal blood, and that crystalloid substances, such as quinine and the salicylates, pass through the epithelium of the placental villi and can be found in the fetal circulation in the same strength as in the maternal circulation.

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10. Torland, T.: Fetal Mortality After Induction of Labor by Castor Oil and Quinine, J. A. M. A. **90**:1190 (April 14) 1928.

11. King, E. L.: Does Quinine in the Induction of Labor Have a Deleterious Effect on the Fetus? J. A. M. A. **101**:1145 (Oct. 1) 1933.

12. Kirby-Smith, J. L.: Personal communication to the author.

13. Porak, C.: L'absorption des médicaments par le placenta, Paris, G. Masson, 1878; J. de thérap. **5**:332 and 412, 1878.

14. Nicloux, M.: Le passage des substances chimiques de la mère au foetus, Obstetrique **2**:840, 1909.

While morphine and the barbital preparations seem to have no predilection for the eighth nerve, I mention them here, for it is germane to the subject to show the permeability of the placenta to drugs and to suggest that they seem to have a like effect on both mother and child. The numerous cases of congenital morphinism furnish evidence that drugs pass from the mother to the child through the placenta. Pettey [15] reported on 6 babies whose mothers were addicted to morphine. He stated that the new-born baby of a mother who is an addict to morphine is as much an addict as the mother, for the child's blood and tissues are as fully saturated with the narcotic as those of the mother. He further declared that every child born of a mother using opium should be given an opiate for the first three days after birth, since severance of the placental circulation through which the child has been receiving the narcotic shuts off the supply, and the shock and collapse incident to the abrupt withdrawal of opiates from an addict follow if the drug is not administered. Burnett [16] made similar observations regarding the treatment of infants whose mothers are victims of morphine addiction.

The use of twilight sleep has been largely abandoned in the practice of obstetrics, owing to the cyanosis of the new-born child, a condition which proves that the drug used to induce this sleep is transmitted from the mother to the child.

At the recent meeting of the American Physiological Society, Dille [17] reported finding a relatively large amount of amytal and veronal in the unborn offspring of guinea-pigs, rabbits and cats which had received doses of these pain-relieving drugs.

DEAFNESS OF THE NEW-BORN FOLLOWING PREPARTUM MEDICATION OF MOTHERS WITH QUININE

In a previous article [18] I reported a case which aroused my interest in the possibility of certain drugs administered to the pregnant mother causing deafness in the infant and which I shall briefly review.

A multipara brought to me her 4 year old child, who had previously been examined by several otologists, each of whom had made a diagnosis of complete nerve deafness. After a thorough examination I concurred in this diagnosis. My examination showed a normal external ear; the drum membrane showed the usual light reflex, no retraction and no displacement of the umbo or malleus. The vestibular responses with the whirling and caloric tests were normal and all the

15. Pettey, G. E.: Congenital Morphinism, with Report of Cases, South. M. J. **5**:25 (Feb.) 1912.

16. Burnett, S. C.: Morphinism in Pregnancy and the Unborn, M. Herald **39**: 161 (July 15) 1920.

17. Dille, J. M.: The Effects of Barbiturates on the Embryo and on Pregnancy, J. Pharmacol. & Exper. Therap. **52**:129 (Oct.) 1934.

18. Taylor, H. M.: Does Quinine as Used in the Induction of Labor Injure the Ear of the Fetus? J. Florida M. A. **20**:20 (July) 1933.

reflexes were normal. The child's general physical appearance showed every evidence of health. The Wassermann reactions of the blood of the father, mother and child were negative, and there was no indication of deafness or consanguinity in the family. The mother related that she had previously given birth to three perfectly healthy children; all the labors had been normal. With this last child, after four hours of labor, she was given castor oil followed by three 10 grain (0.64 Gm.) doses of quinine an hour apart. Three hours later she was delivered of a boy weighing 6 pounds (2,721.5 Gm.). She recalled that half an hour after the second dose of quinine she complained of severe headache, roaring in the ears, increasing deafness and severe itching. She described a breaking out of large purplish swellings on her face, chest and extremities—urticaria. Deafness persisted for about six weeks; otherwise, convalescence was normal. Two years later, when she discovered that her child was deaf, she became convinced that the 30 grains (1.9 Gm.) of quinine which she had taken and which had caused her symptoms and temporary deafness were also the cause of the deafness of her child. A detailed study of additional cases with similar histories will be reported later.

This case led me to undertake an exhaustive survey of the literature for references to the subject of prenatal medication and its relation to the fetal ear. I was able to find only one, a case reported in 1870 by a country physician [19] of Washington County, Ga. His keen observations, made sixty-four years ago, are of sufficient interest to repeat here:

S. T., age about 26 years, had always been healthy up to July, 1867, when she was taken with chills and fever (as that disease was prevalent in this section of the country then) while about two months advanced in pregnancy. She continued to have chills at intervals, until February, 1868, when she was delivered of a female child. Her attending physician, Dr. H., gave her a great deal of quinine and in such large doses that it affected her hearing, and at one time, during a period of three weeks, she was not able to hear at all, but was perfectly deaf. I was called in a short time ago to see the child that was delivered in February, 1868, and soon ascertained from her actions and the statement of her mother, that she was deaf. She is the fourth child, perfectly healthy and sound in every way, except her hearing. She can laugh, cry, and make a noise as loud as any child, but doesn't try to talk, only to herself while at play and then you cannot understand her. I have known the mother and her husband for several years, and have traced their families as far back as I could, and can find no hereditary disease or any cause whatever why this child should be deaf, unless caused from quinine given the mother, and for this reason I have reported the case, in order that someone who has had more experience than I have, may give me some light upon the subject.

Recently, Dr. Paul Eaton, director of laboratories for the State Board of Health of Florida, called my attention to an article by Dr. Fritz Heider [20] of the department of psychologic research of the Clark

19. Roberts, John B.: Does Quinine, Given a Woman While Pregnant, Have Any Effect upon the Foetus? Richmond & Louisville M. J. **10**:238, 1870.

20. Heider, Fritz: The Influence of the Epidemic of 1918 on Deafness: A Study of Birth Dates of Pupils Registered in Schools for the Deaf, Am. J. Hyg. **19**:756 (May) 1934.

School for the Deaf at Northampton, Mass., who secured the dates of birth of several thousand children registered over a period of twenty years, from 1906 to 1925, in sixteen schools for the deaf in the United States. He used these statistics only for the purpose of correlating them with the unprecedented incidence of influenza in 1918, but they also show a definite relationship between deafness and date of birth occurring in the second half of the year for children registered in the schools located south of the thirty-ninth parallel. Data from these schools show that 359 children were born during the first half of their respective years of birth and 849, nearly two and one-half times as many, during the second half, the season when malaria—for which quinine, a known cause of nerve deafness, is the specific—is most prevalent in the South. This seasonal difference in the dates of birth of children in institutions for the deaf is not indicated in the statistics which Heider gathered from schools located in the North, where malaria is rare. The corresponding figures for that section were 1,977 and 2,033, a difference of only 56. It appears, then, that for the children in the northern institutions there was no appreciable relationship between the date of birth and their deafness, but in the southern institutions approximately two and one-half times as many children were born in the second half of the year as in the first half. Heider's figures show that there were 93 dates of birth occurring in the first half of 1918 and 285 in the second half among the children of the southern schools included in the survey. If the figures for this abnormal year are excluded, the dates of birth still remain more than twice as numerous in the second half of the year as in the first half for the period of the remaining nineteen years.

Commenting on Heider's article, Winslow [21] stated that otitis media was a rare sequel of the 1918 epidemic of influenza in the North. This observation could as readily be applied to the South. He stated of the statistical study: "Such a revelation of an important epidemiological factor . . . constitutes a truly dramatic incident in the history of vital statistics." It is a finding of far-reaching significance that in a year when influenza was endemic in the whole United States, a sharp rise in the birth curve of deaf children was discernible and was due largely to the pronounced rise for the children in the institutions of the South. It is singularly striking that in the southernmost schools—those located in Florida and Alabama—the number of deaf children born in the second half of 1918 was seven times as great as the number born in an average half year. That the epidemic reached its peak in this section in the fall of 1918 and that quinine and the salicylates were used freely in these states in the treatment of influenza during the epidemic are well known. Undoubtedly, the expectant mother received her share of these drugs.

21. Winslow: Prefatory note in Heider, Fritz.[20]

It seems, however, equally striking that for the children registered in these sixteen schools for the deaf throughout the United States for the twenty year period from 1906 to 1925 the dates of birth were more than twice as numerous in the second half of the year only among those children in the southern schools, particularly those of Florida and Alabama, where malarial infestation is excessively high and prevails from July to January. The absence of any appreciable relationship between the date of birth and deafness for the children in the northern institutions merely accentuates this finding. The fact that a marked preponderance of dates of birth appeared in the second half of the year for those children only who were registered in the schools for the deaf in the South, particularly in Alabama and Florida, where malaria is markedly prevalent during that half of the year, seems to suggest that the administration of quinine to the pregnant mother during the season when malaria is at its height in the South cannot be ignored as a possible etiologic factor of deafness in the new-born.

Quinine has long retained its popularity with the laity of the South, not only as a specific for malaria in particular and for influenza as well, but as a household remedy. As a preventive of yellow fever in days now gone, as a perennial remedy for the common cold and as a cure for fevers in general, this gift of the Peruvian Indians to the pharmacopeia of today has been taken freely throughout the South, with or without the advice of a physician, and its popularity has not even now entirely waned. Many a pregnant southern mother has no doubt resorted frequently to this drug as a specific for various ailments, turning to it especially in the season when malaria is prevalent.

NEED FOR ACCURATE RECORDS OF PRENATAL MEDICATION IN CASES OF NERVE DEAFNESS

Heider [20] did not differentiate between the incidence of nerve deafness and air conduction deafness in his survey. He mentioned that he found it practically impossible to secure accurate records of the time at which deafness first occurred or of its causes, since this condition frequently passes unnoticed during the first years of life. Perhaps the reason why the otologist has practically ignored the subject of prenatal medication as a possible etiologic factor of deafness in the new-born is that a child must be 2½ or 3 years old before a diagnosis of nerve deafness can be made. By that time the prenatal history has been dismissed. The history which the otologist usually endeavors to get consists principally of whether there has been a family history of deafness, consanguinity, hereditary syphilis or meningitis, and with these details the subject is generally closed. To some, however, the history of the drugs given the mother during pregnancy is of as much importance as whether the patient had a great-uncle or a second cousin who was

deaf. If it were possible to ascertain the incidence of nerve deafness among the children registered in schools for the deaf in the United States, and, by questioning the mothers, to gather information regarding their intake during pregnancy of drugs which may produce nerve deafness, the resultant findings might constitute a dramatic incident in the history of otology.

The whole subject deserves careful investigation. If, over a given period of time, a large number of otologists will manifest sufficient interest when obtaining the history of every child showing nerve deafness to include in the usual questionnaire the history of drugs administered to the mother during her term of pregnancy, prenatal medication may become an established etiologic factor of deafness. Deafness from this cause may then be classified as deafness asquired in utero. This type of deafness may be represented by merely a diminution in the function of hearing and not necessarily by total deafness. Data concerning those drugs used in prenatal medication which have a predilection for the auditory nerve are of particular interest in cases in which the family history contains no record of deafness or consanguinity, and in which the patients show no deformities and give normal vestibular reactions to the whirling and caloric tests, but show on examination complete deafness or partial deafness with tone gaps or islands of deafness.

COOPERATION OF BIOCHEMIST, HISTOLOGIST, OBSTETRICIAN AND OTOLOGIST SOUGHT IN STUDY OF PROBLEM

If the question of prenatal medication as a causative factor of nerve deafness is to be brought out of the domain of theory, the cooperative study of the biochemist, the histologist, the obstetrician and the otologist will be needed. Recently the department of otolaryngology of the College of Physicians and Surgeons of Columbia University designated Dr. E. P. Fowler Jr. to undertake experimentation on animals to ascertain the effect which drugs administered to the pregnant animal may have on the cochlea of the offspring. Whether or not it can be demonstrated that the auditory nerve and the ganglion cells in the ear of the fetus can be injured or destroyed by certain drugs administered to the pregnant animal, it will still be necessary to get on record a considerable number of cases of deafness in which the causative factors appear to be the drugs used in prenatal medication. Due attention to the various aspects of this subject may result in findings which will determine the etiology of a number of baffling and otherwise unexplained cases of deafness in children and thus constitute a truly valuable chapter in the history of otology.

SUMMARY AND CONCLUSIONS

1. Certain drugs have a predilection for the auditory nerve.

2. Idiosyncrasy for drugs may be an important factor in causing nerve deafness.

3. Quinine takes precedence among the drugs causing nerve deafness and is frequently used during the term of pregnancy.

4. Evidence has been presented that certain drugs which have a predilection for the auditory nerve, when administered to the pregnant mother, readily pass through the placenta and may be toxic to the fetus, a possibility which the otologist has virtually ignored.

5. Prenatal medication as a possible etiologic factor of deafness in the new-born is of sufficient importance to warrant the cooperative research of the biochemist, the histopathologist, the obstetrician and the otologist.

111 West Adams Street.

DISCUSSION

DR. JOHN H. FOSTER, Houston, Texas: The effect of drugs on the auditory nerve has long been of interest to me for the reason that I have suffered from a rather marked degree of nerve deafness following the administration of quinine when I was 4 years of age. When I began the practice of otology in Texas twenty-eight years ago, I tested the hearing of hundreds of persons who came from malarial sections. I found that almost every person who had taken quinine to any considerable extent had an appreciable degree of nerve deafness.

With the conviction that I had that quinine was a dangerous drug, so far as hearing is concerned, it puzzled me that I never thought of the danger to the unborn child of the pregnant mother's taking the drug in large quantities. I secured, through the courtesy of the Texas School for the Deaf, the names of the parents of 228 supposedly congenitally deaf children. A questionnaire was sent to each of these parents, embracing the following questions: 1. Do you know of anything that you think may have tended to bring about this deafness? 2. Have there been other cases of deaf-mutism in the family? 3. Did the mother take any quinine during pregnancy or at the time the child was born? (I mean by this sufficient quinine to produce deafness or marked ringing of the ears.)

In response to this questionnaire I received replies concerning 151 cases. The causes of deafness given are listed in the table. I realize that these replies have little real value from a statistical standpoint.

Possible Causes of Deafness in 151 Congenitally Deaf Children

Heredity	33
Consanguinity of parents	2
Injuries at birth	12
Maternal impressions	3
Maternal shock	6
Illness of mother	4
Illness of child during infancy	14
Quinine taken by mother	9
Quinine taken by child	1
Cause unknown	67
Total	151

I wish to commend Dr. Taylor for bringing this subject to attention. I had no idea that quinine was used so extensively in obstetric practice Even though only a small proportion of cases of congenital deafness are due to this drug, the possibility should give pause and the knowledge prevent that number of cases. It is highly important that this danger should be brought to the attention of general practitioners and obstetricians.

Of one thing I am sure: Some cases of congenital deafness are due to the administration of quinine to the mother. In several of the cases mentioned quinine was definitely cited as the cause. The use of quinine in certain districts is so common as to excite no notice.

I should like to stress the point made by Dr. Taylor that a large number of persons have a marked idiosyncrasy for quinine and in such persons the administration of even 10 grains (0.64 Gm.) produces more effect than ten times as much in another.

The preponderance of deafness in children born in the summer and fall, mentioned by the essayist, is significant.

Dr. Robert Mussey, Rochester, Minn.: Dr. Taylor has raised a most interesting question. For many years quinine has been used as a method of inducing labor. There is a question in the minds of some observers as to its value in this. For instance, King, in his paper of last summer on the use of quinine in the induction of labor, in which a fetal death due to it was reported, quoted Williams and also Solomon, who stated that they did not believe that quinine was of much value in the induction of labor, but that it did intensify the pains of labor. He also quoted Dodek, who believed that the oxytocic value of quinine had been overestimated, and Bourne and Berne, who thought that the drug had little effect.

Thus, there is some difference of opinion as to the effect of quinine when used to induce or to intensify the pains of labor. However, as Dr. Taylor has stated, fetal deaths have been recorded as resulting from the use of this drug, and a number of observers have found that the incidence of the appearance of meconium in the amniotic fluid is definitely higher in women who have had quinine during labor. Among those who noted this are Porak, in 1878, Dille, King, Saddler and Dilling and Gemmell. Last summer, Dr. Lillie called my attention to Dr. Taylor's previous paper, and later I had the opportunity of reading Dr. King's paper.

For a number of years I have used quinine in the induction of labor, 10 grains (0.64 Gm.) every hour for three doses. For quite a few years I have not used more than a total dosage of 20 grains (1.3 Gm.) in the induction of labor, because it was noticed that the larger dosage caused several patients to have tinnitius and other auditory disturbance. However, because of the case made out against the use of quinine by Dr. Taylor and Dr. King, I have discontinued its use in the induction of labor.

I took occasion to inquire about 35 deaf children or children who had at least a deficiency of hearing who have attended special classes for deaf children in Rochester during the past ten years, and I know of only one child among them whose mother had quinine in the induction of labor.

The query that Dr. Taylor raises is correct: otologists have not gone into these cases as carefully as the otologist probably will in the future, and as I hope the obstetrician may.

Dr. Taylor has made out a good case against the use of any drug taken in the prenatal period which may affect the fetus in a deleterious way, and I agree with him that further investigation of this subject should be carried on. I do not think that one can bring a blanket indictment against quinine or any other drug until further investigation is made.

DR. BURT R. SHURLY, Detroit: The timely paper of Dr. Taylor deals with the field of preventive otology, in which otologists are scientifically weak and in which more research is needed. Collective investigation in children has shown that approximately 62 per cent of all deafness is congenital.

The key to prevention is the nutritional, biochemical and hematologic study of the pregnant mother. Experiments carried out in the research laboratory and endocrine clinic of the Detroit Medical College have shown how important the prenatal administration of iodine and thyroid extract is in the prevention of congenital hyperthyroidism. Much has been written on the value of halibut liver oil, vitamins A and D concentrated with the proper ratio of calcium and phosphorus, ultraviolet rays and sunshine in rickets and bony deformities. The importance of thorough treatment of the syphilitic mother is well understood and is practiced by physicians generally.

Idiosyncrasy for drugs is well recognized in the case of alcohol, quinine, belladonna and the salicylates, and the experienced patient promptly informs one of it. Quinine is used more in the South than in the North.

It is well established that fetal circulation is highly sensitive to medication and biochemical change. Fineberg, in 1932, advanced the theory that hypercholesteremia may be the missing etiologic link in the chain formed by essential hypertension, arteriosclerosis, apoplexy and chronic progressive senile deafness. Sixteen rabbits were fed chemically pure cholesterol three times a week for a period averaging seventy days. The dose was from 5 to 10 cc. of a 20 per cent oil solution of cholesterol. Artificial hypercholesteremia was produced in the rabbits. All showed practically the same histopathologic change in the temporal bones, with a difference of degree proportionate to the period of time of the feeding of cholesterol. Control animals showed no fatty or lipoid changes in the ear. Fineberg concluded that the experimental evidence obtained establishes clearly that cholesterol metabolism plays a large rôle in certain types of internal ear deafness. A high cholesterol content in the blood of mothers during the prenatal state may be a factor in the cause of deafness in the new-born.

Cretins apparently do not demonstrate an increased percentage of deafness. Barlow's study and my own on vitamin deficiencies do not show a selective action on the eighth nerve.

The obstetrician and the pediatrician, as Dr. Taylor has said, must collaborate in the confirmation of these deductions. At present the suggestions are based on an unproved theory. Just as the mother believes that a fall has been responsible for every congenital lesion of the brain and cerebral injury of the child, so the ascribing of deafness in an infant to the administration of a drug in pregnancy may be a way to relieve the mind of the mother from all blame. The paper is a stimulation to the obtaining of better histories and to further laboratory and clinical study. The increase in the use of quinine in the South is significant and will bear further study.

As one reads the report of Taylor's and of Hart's cases, one is impressed with the facts of idiosyncrasy for quinine, but it is only fair to say that when one carries on a study without laboratory or research findings one can express a suspicion only. The deductions are the result largely of clinical observation in a few cases. The profound influence of chronic alcoholism and the bad effects on the offspring are well recognized by the laity as well as by physicians.

Quinine is used extensively in the induction of labor for one day, yet it is unproved that the toxic effect or the idiosyncrasy is in direct relationship to con-

genital deafness, as congenital deafness may be ruled out in thousands of births in which much quinine was used.

The paper calls for a further survey or a collective investigation and collaborative research as planned. Until then, one may add this question in taking histories and await additional information from the laboratory and the pathologist.

DR. R. G. REAVES, Knoxville, Tenn: After talking with Dr. Taylor at the meeting of the Southern Medical Association in Richmond last fall and learning of his interest in the prenatal use of certain drugs as a possible cause of congenital deafness, I decided to carry out some investigations along this line. As otologist to the Tennessee School for the Deaf, I had a number of questionnaires sent out from the school to the mothers asking the following questions: 1. Did you take quinine during your pregnancy or during labor? 2. Did you take much acetylsalicylic acid for any cause? 3. Were you treated for rheumatism? 4. Did you use alcohol in any form? 5. Did you use tobacco in any form? 6. Did you have malaria or any other illness during your pregnancy? 7. Please give the name and address of the physician who attended you. 8. If it is convenient for your physician, we shall appreciate his helping you fill out this blank and giving any other information that he may believe would benefit us.

Ninety-two replies were received, 46 of which were negative and 46 affirmative (table).

Statistics for Fifty-Eight of Ninety-Two Mothers of Congenitally Deaf Children Who Used Drugs During Pregnancy

Quinine (4 used chill tonics for malaria)	15
Acetylsalicylic acid	8
Treated for rheumatism	2
Used alcohol	1
Used tobacco	17
Morning sickness, took much medicine	1
Ill all the time	1
Influenza for 3 months	1
Measles	3
Mumps	3
Epilepsy; took alcohol	1
Influenza	3
Pneumonia with temperature of 104 F. when child was born	1
Took wine of Cardui	1
Total	58*

* The total number of fifty-eight means that some of the forty-six used more than one drug during pregnancy.

Of the 92 mothers who replied, 17 per cent had used quinine, 8.7 per cent acetylsalicylic acid and 3.2 per cent alcohol and 18.5 per cent tobacco.

Illness with the possibility of toxicity from the disease or of the taking of medicine that would affect the fetus was present in 15.2 per cent.

From this analysis it is readily seen that damage to the auditory nerve of the fetus may have resulted from the drugs or the toxins of diseases to which the mother was subject during pregnancy. I have no definite information as to the amounts of the drugs taken and therefore cannot draw any definite conclusion as to what part these played in the cause of the congenital deafness in these cases. It is also interesting to note that 15.2 per cent of the mothers either had illness, with the possibility of a toxic condition sufficiently severe to affect the auditory nerve of the fetus, or took some drug during illness that affected the nerve.

Dr. Taylor referred to Dr. Fritz Heider's investigation of the dates of birth of deaf children born in 1918 and his finding that about two and one-half times as many of the births occured in the latter half of the year as in the first half in the South, and called attention to the fact that quinine is used more prevalently in the latter half of the year. He did not say, however, whether this investigation covered all deaf children or only the congenitally deaf. I made an investigation at the Tennessee School for the Deaf, with the following results: Of 327 deaf children registered for 1933 and 1934, 184 had congenital deafness, and 114 had acquired deafness. Of the 184 (56.3 per cent) congenitally deaf children, 78 (42.4 per cent) were born in the first half of the year and 106 (57.6 per cent) in the latter half. Of the 114 children with acquired deafness, 57 (39.9 per cent) were born in the first half of the year and 86 (60.1 per cent) in the latter half.

My enthusiasm for statistics diminished somewhat when I found that the percentage of dates of birth in the latter half of the year was higher for the children with acquired deafness than for those with congenital deafness. Therefore, I believe that further investigation is necessary along this line before attributing the increase in the dates of birth in the latter half to the prenatal use of quinine.

Dr. Taylor spoke of ascertaining the incidence of nerve deafness among children registered in schools. Nerve deafness among children registered in the Tennessee schools is far above 90 per cent in both those with acquired and those with congenital deafness. Furthermore, quinine and the antipyretics given to young children for influenza and other diseases may cause or contribute to the acquired deafness of the children. This phase should be investigated along with the other.

Dr. H. Marshall Taylor, Jacksonville, Fla.: This subject is too broad for one person to solve, and I am asking for cooperation in the study of its various phases.

Dr. Reaves has probably drawn his deductions from data obtained for the mountainous area of east Tennessee. I doubt whether there is as much malarial infection there as in the more southern states.

Dr. Shurly spoke of using the dog for experiments. It has been shown by other investigators that the placenta of the dog seems to destroy drugs. He will find the cat, rat and guinea-pig better animals for this investigation.

Much light can be thrown on this subject if every member will endeavor to get the history of the prenatal medication of the mother of every patient suffering from nerve deafness.

INCIDENCE OF ALLERGY IN RHINOLOGIC PRACTICE

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It has seemed to me that the frequency with which allergic manifestations appear in rhinologic practice is not recognized, and that the diagnosis of nasal allergy is largely neglected by rhinologists. The prevalence of sinus disease, as such, has been sharply emphasized in rhinologic literature during recent years, but it is startling to see the number of papers on diagnosis and surgical intervention in sinus disease from which even the barest mention of allergy is omitted. One is forced to conclude that allergic changes in the membranes of the nose and sinuses are rarely seen in the practice of many writers, and I have been surprised to note that many papers on sinus disease as a cause of asthma and other bronchial involvements have failed to suggest that some of the changes seen in the mucous membranes might be allergic.

In making these observations I do not wish to ignore the contributions to the literature of nasal and sinus allergy which have been made by rhinologists and allergists, such as Goodale,[1] Spain,[2] Vaughan,[3] Hastings,[4] Piness and Miller,[5] Eyermann,[6] Balyeat,[7] Rowe,[8] Rackemann and Tobey,[9] Rackemann,[10] Duke,[11] Hansel,[12] Coates[13] and Dean.[14]

1. Goodale, J. L.: Diagnosis and Management of Vasomotor Disturbances of the Respiratory Air Passages, Tr. Am. Laryng. A. **38**:82, 1916.

2. Spain, W. C.: The Diagnosis and Treatment of Atopic Coryza (Perennial Hay Fever), Ann. Otol., Rhin. & Laryng. **34**:1093, 1925.

3. Vaughan, W. T.: Diseases Associated with Protein Sensitization, Virginia M. Monthly **49**:316 (Sept.) 1922.

4. Hastings, H.: Allergic Conditions of the Nose and Throat: Clinical Consideration, Tr. Am. Laryng. A. **52**:241, 1930.

5. Piness, G., and Miller, H.: The Importance of Food Sensitization in Allergic Rhinitis, J. Allergy **2**:73, 1931.

6. Eyermann, C. H.: Nasal Manifestations of Allergy, Tr. Am. Laryng., Rhin. & Otol. Soc. **33**:477, 1927.

7. Balyeat, R. M.: Allergic Diseases: Their Diagnosis and Treatment, Philadelphia, F. A. Davis Company, 1930.

8. Rowe, A. H.: Food Allergy, Philadelphia, Lea & Febiger, 1931.

9. Rackemann, F. M., and Tobey, H. G.: The Nose and Throat in Asthma, Tr. Am. Laryng., Rhin. & Otol. Soc. **35**:258, 1929.

10. Rackemann, F. M.: Clinical Allergy, New York, The Macmillan Company, 1931.

11. Duke, W. W.: Allergy, Asthma, Hay Fever, Urticaria and Allied Manifestations, St. Louis, C. V. Mosby Company, 1926.

(Footnotes continued on next page)

Their work has been outstanding and will undoubtedly have a far-reaching effect, but physicians still fail to appreciate the importance of allergic manifestations in the nose, and rhinologists do not yet recognize and diagnose sensitization reactions in the nasal and sinus membranes as frequently as they should. It is true that hay fever and vasomotor rhinitis are generally recognized as allergic diseases, but with these exceptions nasal and sinus allergy is largely ignored.

Such a diagnosis as diseased sinuses or sinusitis is common, but too frequently the diagnosis is not properly analyzed to ascertain the true nature of the disease, which is often allergic. This might be excusable if the incidence of allergy in rhinologic practice were actually a rarity, or if allergy ordinarily were especially difficult to diagnose, but such is not the case.

With the idea of making a fair estimate of the incidence of allergy in rhinologic practice, I have analyzed the records of my last 2,000 patients. Of these, 700 came with primary nasal complaints or were referred for examination of the nose and sinuses as possible sources of involvement elsewhere in the body. Of the 700 cases, 245 were surgical and 455 nonsurgical. In the surgical group a diagnosis of some form of nasal or sinus allergy was made in 65, or nearly 26.3 per cent. In the nonsurgical group, 126, or about 27.75 per cent, showed evidence of nasal or sinus allergy. In the entire 700 cases, therefore, both surgical and nonsurgical, 191, or approximately 27.3 per cent, were, according to my diagnosis, allergic.

The association of nasal and sinus allergy with other allergic conditions in the 126 nonsurgical cases is shown in table 1. Some patients gave a history of hay fever or other allergic manifestations which were not present or complained of at the time of examination and hence are not mentioned in the table.

The allergic changes in the nasal mucous membranes included in table 1 under the title of nasal allergy are: edema of the nasal mucosa; polypoid hypertrophy of the turbinates, and polypi having their origin in the accessory cavities.

The frequency with which involvement of the sinuses was diagnosed roentgenographically in the 126 cases is shown in table 2. Confirmation by means other than roentgenogram was resorted to in many cases, but not in all. As it is not practical or necessary to enter into a detailed discussion of the roentgen observations, all pathologic change in the

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12. Hansel, F. K.: Clinical and Histopathological Studies of the Nose and Sinuses in Allergy, J. Allergy **1**:43, 1929.

13. Coates, G. M.: The Rhinologic Aspects of Allergy, Tr. Am. Laryng., Rhin. & Otol. Soc. **32**:383, 1926.

14. Dean, L. W.: Recent Advances in Oto-Laryngology: Medical and Surgical Treatment, Ann. Otol., Rhin. & Laryng. **38**:952, 1929.

sinuses is classed under one general term, without attempting to differentiate as to grade, type or location. The findings ranged from slight edema of the lining mucous membrane in a single sinus to extreme polypoid hyperplasia filling all the cavities.

Table 2 indicates that a high proportion of nasal allergic conditions also show involvement of the sinuses when studied roentgenographically. In 8 cases secondary suppuration was present in one or more of the

TABLE 1.—*Association of Nasal Allergy with Other Allergic Conditions in Nonsurgical Cases*

Type of Pathologic Process	Number of Cases
Nasal allergy alone (exclusive of pollinosis)	59
Pollinosis (hay fever) alone	20
Nasal allergy with asthma	29
Nasal allergy with bronchitis and/or bronchiectasis	9
Nasal allergy with headache	3
Nasal allergy with arthritis	3
Nasal allergy with skin lesions	2
Nasal allergy with angioneurotic edema	1
	126

TABLE 2.—*Roentgen Observations in Nonsurgical Allergic Cases*

Pathologic changes in sinuses	98
Negative roentgenographically	13
Not examined roentgenographically	15
	126

TABLE 3.—*Association with Other Allergic Conditions of Surgical Allergic Cases*

Type of Pathologic Process	Number of Cases
Nasal allergy alone (exclusive of pollinosis)	37
Pollinosis (hay fever)	3
Nasal allergy with asthma	15
Nasal allergy with bronchitis and/or bronchiectasis	4
Nasal allergy with headache	4
Nasal allergy with skin lesions	1
Nasal allergy with angioneurotic edema	1
	65

cavities, 2 showed serous fluid and 3 were doubtful. Thus, in only 10 of the 98 cases of demonstrated involvement of the sinuses was fluid undoubtedly present. Even in the 10, thickening of the membranes was also demonstrable roentgenographically. In the other 88 cases the pathologic process was of the so-called hyperplastic type, which means that the mucosa was the seat of an edematous thickening, a typical allergic manifestation.

The association with other allergic conditions in the surgical series of 65 cases is shown in table 3.

A still higher proportion showed evidence roentgenographically of a pathologic process in the sinuses, as indicated in table 4.

Secondary suppuration was present in 17 of the 50 cases showing roentgen evidence of a pathologic process in the sinuses. Six of the 17 were among the 15 patients with asthma. Thorough drainage was established in each case, but with no permanent beneficial effect on the asthma.

In the series of 65 surgical cases, ninety-two operations were performed, as shown in table 5.

The results of surgical intervention in this series were, on the whole, satisfactory. Removal of obstructive polypi and turbinal hypertrophy seems to improve not only the breathing space, but the allergic symptoms, at least temporarily. In many cases this alone is sufficient to

TABLE 4.—*Roentgen Observations in the Surgical Allergic Cases*

Pathologic changes in sinuses	50
Negative roentgenographically	6
Not examined roentgenographically	9
	65

TABLE 5.—*Operations Done in Sixty-Five Surgical Allergic Cases*

Operation	Number
Removal of polypi and turbinal hypertrophy	42
Submucous resection	28
Operation on sinuses	22
	92

satisfy the patient. Submucous resection often results in similar improvement. Surgical intervention in the presence of pus is of value in removing the signs of suppuration, but I have yet to see it serve the purpose of removing a suspected focus of infection. Needless to state, the underlying allergic disease remains and continues to produce its symptoms after any form of nasal operation, however skilfully performed.

The series of surgical cases emphasizes the fact that allergic patients frequently have primary nasal involvement requiring correction by operation, the symptoms of which are accentuated by the allergic condition. Allergic manifestations often bring these patients to seek relief, which may be obtainable only by means of needed surgical intervention, in addition to treatment of the allergy. Also, many purely allergic phenomena become susceptible to surgical intervention, notably obstructive polypoid hypertrophy. In addition, associated infection may be engrafted on an allergic base and result in suppurative disease in the

sinuses. Surgical intervention is not, of course, withheld in these instances simply because the patient is allergic, but should be carried out in accordance with sound surgical principles. On the other hand, allergic membranes should not be removed to cure allergic disease, as manifested either locally in the nose and sinuses or in its more remote locations, such as the bronchial tree in asthma.

Tables 6 and 7 combine the data on the 191 allergic cases, both surgical and nonsurgical. Of the 191 allergic cases, 167 were studied roentgenographically, and 148, or nearly 89 per cent, showed evidence of involvement of the sinuses. However, it must be borne in mind that even minor instances of pathologic change in the sinuses were

TABLE 6.—*Association of Nasal Allergy with Other Allergic Manifestations in the Entire Series*

Type of Pathologic Process	Number of Cases
Nasal allergy alone (exclusive of pollinosis)	96
Pollinosis (hay fever)	23
Nasal allergy with asthma	44
Nasal allergy with bronchitis and/or bronchiectasis	13
Nasal allergy with headache	7
Nasal allergy with skin lesions	3
Nasal allergy with arthritis	3
Nasal allergy with angioneurotic edema	2
	191

TABLE 7.—*Roentgen Observations in the One Hundred and Ninety-One Cases of Nasal Allergy*

Pathologic change present in sinuses	148
Negative roentgenographically	19
Not examined roentgenographically	24
	191

included as positive, because the sinuses in allergic nasal disease are frequently the seat of a slight degree of mucosal thickening of the same type as that found in the nose. On the other hand, many examples of extreme involvement were also found, and cases of the latter type were somewhat in the majority. That edematous change of some degree is to be found in the sinus mucosa in almost every instance of nasal allergy is, therefore, clearly shown.

Of the 148 cases of sinus involvement in the series, serous fluid was found in 2, and in 25, or over 17 per cent, the sinuses proved to be the seat of suppuration. This is not surprising, as the nature of the pathologic change predisposes to secondary infection, although the lesions themselves are primarily nonsuppurative. The edema of the membranes naturally reduces their resistance to infection, in addition to obstructing the ostia of the cavities and interfering with the efficiency

of ciliary action. Thus, when edema favors stasis, secondary infection becomes a most logical sequel.

These figures indicate a remarkably high incidence of allergy in the nasal mucous membranes. There is probably no other rhinologic disease which is comparable to it in frequency, and therefore the subject of allergy is important to the rhinologist, who should be alive to the possibility of the presence of allergy in every case of nasal involvement. He should be on the lookout for symptoms and be prepared to diagnose it, and he should also know the conditions under which allergy is likely to appear, the diseases with which it is likely to be associated and its relation to them.

Of the cases coming directly to the rhinologist which are or may be allergic, the first to be mentioned should be those of hay fever and vasomotor rhinitis. These are strictly nasal complaints. The history of seasonal onset in hay fever and the perennial nature of vasomotor rhinitis, combined with the symptoms of obstruction, sneezing, watery discharge and lacrimation, should make the diagnosis simple. In addition, there is the appearance of the membranes, which is that of paleness with edema, so typical of all allergic conditions in the nose.

Asthmatic patients are usually referred to the rhinologist for nasal examination in the hope that sinus disease may be found and eradicated, for the purpose of curing the asthma. All such cases should be approached with the expectation of finding allergic manifestations in the nose and sinuses. The manifestations take the form of the usual edema and paleness of the membrane, with polypi appearing frequently and with edematous thickenings of various grades in the membranes of the sinuses—most frequently in the antrums and ethmoids. The removal of the edema should not be expected to cure the asthma. Rather, it would seem logical to examine and treat the nose and sinuses in asthmatic patients with the idea that the nasal findings may conceivably be manifestations of the patient's known allergic state and not a cause of it. This attitude will obviate many disappointments and make for a more perfect understanding of nasal and sinus pathologic processes in asthma.

In the so-called bronchosinus cases, the sinus and bronchial pathologic changes have been linked etiologically for several years, and it is true that frequently acute, subacute and chronic bronchial conditions are found in association with involvement of the sinuses. In most such cases, especially in the subacute and chronic ones, the groundwork has been laid by allergy, both in the bronchi and in the sinuses. Here again I believe is an example of associated lesions, not of an etiologic relationship. The bronchial lining membranes are almost identical histologically with those of the upper respiratory tract and this, in addition to their continuity, makes them susceptible to similar pathologic changes and to the same infections. Many of these patients are funda-

mentally allergic, and the allergic edema of the sinus and bronchial membranes reduces their resistance making them more subject to infection and less able to recover from it when it is present. A large percentage of chronic bronchial cases of all types show antral and ethmoidal involvement. The pathologic process in the sinuses is usually edema, with or without a suppurative process engrafted thereon. Surgical intervention is not indicated except in the presence of suppuration, regardless of the extent of thickening of the sinus mucosa. The patients should, however, be carefully studied and treated, for if not treated, especially in the case of children, asthma or chronic bronchitis may develop, often with bronchiectasis, the pathologic changes all resting primarily on an allergic base.

Less frequently, nasal allergic manifestations are met in the search for foci of infection as a cause of various other diseases which are also allergic. This applies to certain conditions of the skin, as eczema, angioneurotic edema and urticaria, now considered by most authorities to be allergic manifestations, a few cases of allergy of the joints, and occasional cases of abdominal allergy. In all these conditions the fact that foci of infection are rare in the nose and sinuses, and that such foci are not the cause of allergy, should be kept in mind. The rhinologist is not called on to diagnose allergic disease in remote organs of the body, but if such cases come for nasal examination and signs and symptoms are suggestive of allergy, it is incumbent on him to transmit that knowledge to the attending physician. Such patients, with a history suggestive of allergy in themselves or their antecedents, should be carefully examined for nasal manifestations of the condition. In many, the signs and symptoms of allergy will be prominent. The symptoms usually constitute so-called catarrh, as diagnosed by the patient, and are often thought to be indicative of disease of the sinuses. On examination the membranes may present the characteristic color and edema of allergy, and the presence of nonpurulent mucoid secretion may be a further aid in diagnosis.

Headache is also a symptom which frequently brings the allergic patient to the rhinologist. The patient and his physician concur in the opinion that the headache may be caused by the sinuses, and this may be true in rare cases. More frequently, however, allergy is at the bottom of the trouble, usually in the form of sensitization to certain foods.

In every instance of suspected nasal and sinus disease roentgenograms must be utilized to complete the examination. As shown in the tables, frankly allergic nasal conditions will nearly always show a pathologic process in the sinuses on roentgen examination; other allergic states just enumerated may show it. In allergic patients the pathologic process may, of course, be primary suppurative disease of the sinuses,

but usually it is simply the edematous membrane of allergy, sometimes swollen to the extent of filling the cavity or extruding through the ostium into the nose in the form of polypi.

In addition to the methods of diagnosis already outlined, microscopic study of sections and tissue will aid greatly in making a diagnosis. The method of examination of the cellular content of the nasal and sinus secretions in allergic cases is simple, and consists of the examination of a direct smear stained with Wright's or Giemsa's stain. The characteristic cell of allergy is the eosinophil, frequently present in large numbers in the nasal secretions of allergic patients. It is true that the presence of eosinophils, either in the blood stream or locally in the tissues, cannot be accepted as pathognomonic of allergy. They are present in many other conditions, notably in parasitic infections, but it must be recognized that eosinophils are not normally present in the nasal tissues and secretions, and experience proves that they are often present in the nose in nasal allergy, especially during its acute manifestations. On the other hand, the absence of eosinophils from the nasal secretions in suspected cases should not be taken as final proof of the absence of allergy, for I have frequently observed that eosinophils may be conspicuously absent from both the blood and the secretions in known cases of nasal allergy. However, when found, it is appropriate in the present state of knowledge that one accept them as indicative of an allergic process. Eosinophils vary in number in different cases, being overshadowed by polymorphonuclear neutrophils in suppurations engrafted on allergic conditions, although even in these their presence is often sufficient to clinch a doubtful diagnosis.

Biopsy may also be resorted to in doubtful cases. It reveals the characteristic serous infiltration of allergic edema in the tunica propria of the nasal and sinus mucosa, usually with eosinophils present in large numbers. Some fibrous hyperplasia will be seen in the chronic cases, and since lymphocytes are normally present in these tissues they can always be expected to accompany the eosinophils, with the addition of a moderate number of plasma cells.

This brief diagnostic outline could be greatly amplified, and the subject of treatment might be gone into. However, it must suffice to say that the treatment of allergic conditions is based primarily on detection of the offending allergens with their withdrawal, or desensitization to them. These allergens may prove to be inhalants, as pollens and a variety of dusts, dermal allergens or ingested substances, including the most common foods. Surgical intervention is definitely contraindicated as a primary method of treatment in the nasal manifestations of allergy, although, as already shown, it has its place within certain limits. Briefly, the limits restrict surgical intervention to the removal of obstructive allergic edema and hyperplasia, as polypi and polypoid hypertrophy of

the turbinates, the drainage of secondarily infected sinuses and the removal of mucosa which has become the seat of suppurative disease. The latter is occasionally found in greatly thickened edematous lining membranes in which dilated mucous glands have become infected, with the formation of subepithelial abscesses.

Finally, I wish to emphasize that according to my experience, focal infection from the nose and sinuses is exceedingly rare and nasal and sinus allergy exceedingly common. However, the former diagnosis is made much more frequently than the latter. There is a tendency to class every deviation from the normal under the one generic term of sinus disease, apparently without thought of the possibility that the condition might be allergic. This is distinctly wrong, and is an error to be avoided, especially in view of the fact that this study has revealed that about 89 per cent of nasal allergic cases will show allergic change of some degree in the membranes of the sinuses. I feel, therefore, that in every instance of suspected focal infection from the sinuses an attempt should be made to differentiate between allergic sinus disease and bacterial invasion, with careful consideration of the possibility that the nasal condition and the original complaint may be no more than concomitant manifestations of the same hypersensitiveness.

SUMMARY

1. In the normal course of rhinologic practice approximately 27.3 per cent of all patients with nasal complaints may be expected to exhibit some form of allergy in the nose, and of these, about 89 per cent will show allergic changes in the sinus mucosa.

2. A better understanding of allergic nasal and sinus disease on the part of rhinologists will prevent frequent errors in the diagnosis of suspected focal infections.

3. A realization of the true relation of nasal and sinus allergy to other allergic manifestations throughout the body will enable the rhinologist to avoid many useless and damaging operations, with destruction of innocent and valuable tissue under the mistaken assumption that dangerous foci of infection are being removed.

510 Republic Building.

SINUS HEADACHE

DIFFERENTIATED FROM HEADACHES OF OTHER ORIGIN

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This brief article can deal but casually with the outstanding features of pain primarily due to sinusitis and enumerate some of the most common causes of headache due to other constitutional disorders.

It is sometimes difficult to distinguish between the pains of sinusitis and those due to other causes. Authorities such as Skillern,[1] Hajek [2] and others have lamented the fact that far too frequently the sinuses have been operated on, and later it has been found that an intracranial or other type of lesion had been the source of the pain. Recently there has been an increasing tendency to assume too readily that obscure pains in the head are of sinusal origin and to forget that sinusitis may exist without pain. The degree of the severity of pain is not a reliable index of the seriousness of the disease. In sinusitis the absence of pain proves nothing, while its presence is important and helpful in making a diagnosis.

All headaches can be classified as mechanical, toxic or reflex.

Pain in the sinuses, in general, may be considered either acute or chronic. There are certain characteristics, regardless of the sinus involved. The pain is due to stimulation of the trigeminal nerve and its associated sphenopalatine ganglion. The wide distribution of this nerve, its connections with a large number of the cranial and sympathetic nerves and the great anatomic variations of the sinuses explain how pains in the head can be so deceptive and so severe.

In acute sinusitis there are two general types of pain: (1) the neuralgic type and (2) a constant type, more or less localized in the region of the diseased sinus. The neuralgic type of pain is periodic. It is invariably present during the morning and gradually disappears before early afternoon. This pain may be followed by a sensation of fulness and pressure in the sinus. The pain begins in the sinus, but may be so severe as to involve adjacent nerves.

The second type of pain in acute cases is constant discomfort in the region of the sinus. It is due to involvement of the mucous mem-

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Read at the meeting of the Jefferson Society for Clinical Investigation, May 17, 1934.

1. Skillern, R. H.: The Catarrhal and Suppurative Diseases of the Accessory Sinuses of the Nose, Philadelphia, J. B. Lippincott Company, 1923.

2. Hajek, M.: Pathology and Treatment of the Inflammatory Diseases of the Nasal Accessory Sinuses, St. Louis, C. V. Mosby Company, 1926.

brane or bony wall of the sinus. There is usually marked stagnation of secretions, and the sinus is sensitive to palpation. The pain may be a dull ache or soreness, becoming at times more intense.

In chronic sinusitis the headache is more diffuse and often indefinite. The violence of the pain bears little relationship to the severity of the infection. There may be a feeling of dulness and heaviness, dizziness or inability to concentrate. There may be freedom from pain for days or weeks. The pain may be intensified by sudden jars, stooping, severe mental or physical effort, loss of sleep, constipation or dietetic indiscretions. Acute exacerbations due to "colds," causing temporary increase of pain, may be frequent, giving the semblance of periodicity. The acute exacerbations are always accompanied by pain in the same region with each recurring attack.

Although the localization and characteristics of pain are not constant, there is a tendency toward such constancy in the individual sinuses.

Early acute maxillary sinusitis usually causes the sensation of pressure, fulness and distention in the sinus. The pain may be a dull ache or may be neuralgic. There is a great tendency to have the pain referred to the frontal region, causing the unwary to diagnose it wrongly as due to frontal sinusitis. Pain is felt in the upper jaw and teeth. The teeth may feel tender, loose or elongated. Continuous pain directly in the sinus usually indicates severe changes in the mucous membrane or bony wall. The pain is increased by jarring, stooping, coughing, sneezing, sudden movements of the head and the excessive use of alcohol and tobacco. There is a tendency toward exacerbations for several days after spontaneous drainage has started.

The symptoms of chronic maxillary sinusitis may be mild or severe. The patient may have no pain to warn him of infection. In fact, pain is often not present in chronic cases, even with severe involvement. When the sinus is filled with polyps, cysts or a tumor, there is sometimes a feeling of fulness or distention. Pain, when present, most often takes the form of infra-orbital or frontal headache. At times the entire affected side of the head feels dull, and there are occasional twinges of neuralgia-like pains in the side of the face and forehead. These pains are most marked in the morning. When there is severe involvement of the walls of the sinus, the local pain may be intense. Tenseness is present almost constantly, and at times there are paroxysms of severe neuralgic pain. This can become so severe as to give the impression that all the sinuses are involved. Sudden motion increases this pain.

In acute frontal sinusitis headache is the most prominent and constant symptom. It is most severe during the morning, gradually subsiding toward noon. It is present from the beginning of the infection and remains in some degree until resolution or chronicity occurs. The

pain is in the sinus and along the supra-orbital nerve. As the disease progresses the pain may radiate to the entire half of the head and involve the collateral branches of the fifth nerve, radiating to the eye, root of the nose, temple, occiput or vertex. In mild cases or in the early stage the pain is one of tension and pressure. As the infection increases there are severe pressure and throbbing, lancinating neuralgic pains that are incapacitating and cause the patient to hold his head and groan with agony, making him feel that suicide would be a welcome solution. These severe pains usually have recessions of short duration and are easily brought on by some slight activity, such as sneezing, coughing, stooping, sudden motion or intense emotion. During remissions there may be a sensation of dulness and heaviness.

In chronic frontal sinusitis there may be no pain, even with marked changes in the mucous membrane and bony walls, or there may be pain almost as severe as in acute cases. The pain is invariably over the region of the sinus. There is a slight numbness, heaviness or tension. The pain is not diffused, as in the other sinuses. In severe cases there is intense, splitting, sickening pain, with throbbing at each heart beat, similar to the pain in meningitis. This pain is due, as a rule, to overindulgence in food or drink, or precedes the appearance of an impending complication. Neuralgic pain is not common in chronic frontal sinusitis, except in acute exacerbations. Patients with this condition may have long intervals of freedom from pain, but are subject to protracted headache due to trivial causes, such as strenuous physical or mental exertion, reading or undue excitement. Alcohol and tobacco are frequently cited as excitants in both acute and chronic cases, but my observations have not substantiated this finding in chronic sinusitis. The vacuum type of headache, described by Sluder, causes intense pain in the frontal sinuses at times and is made worse by movements of the eyeballs.

Acute ethmoid sinusitis can cause pain that is difficult to distinguish from that due to frontal sinusitis. The pain may be a dull pressure or an intense headache. Involvement of the anterior cells causes dull pain between the eyes at the root of the nose. This type of pain can also be due to intranasal pressure. Burning in the eyes, lacrination and increase of pain when the eyes are used for long periods are typical. The pain is steady, without severe exacerbations, in contradistinction to pain in the frontal sinuses. When the posterior ethmoid cells are involved, there is temporal, occipital or parietal headache, which is increased by using the eyes. There may be no pain in the region of the sinus, but in occasional cases pain is referred to the various divisions of the fifth nerve. Pain is most often present along the first, and at times the maxillary, division of the nerve, causing pain in the face that can be confused with that of an antral lesion or tic douloureux. It is not unusual for the symptoms of tic douloureux to be relieved when various sinus infections are remedied.

In acute sphenoid sinusitis the pain may be an intense sensation of pressure deep in the head, in the posterior half of the head or behind the eyeball, over the vertex, just behind the mastoid process and even in the middle ear. The pain over the vertex later becomes a feeling of weight and oppression. Occasionally there is pain in the supra-orbital region. As a matter of fact, the pain in sphenoidal infections is inconstant and of less diagnostic aid than that in any other type of sinus infection.

The pain in chronic sphenoid sinusitis is unreliable. It most often is a feeling of pressure and fulness deep in the head and occipital region, with sometimes stiffness of the neck. Pain in the vertex or temple is frequently present. At times there is numbness in the head, dizziness or a faint feeling on stooping. Infection of the sphenoid and that of the posterior ethmoid sinuses often occur together, making it difficult to tell which sinus causes a specific pain. It should be remembered that often there is infection of more than one group of sinuses, and the headache is then due to a combination of their pain stimuli.

HEADACHE DUE TO CONDITIONS OTHER THAN SINUS DISEASE

A brief review of some of the headaches due to other conditions than sinus disease shows points of similarity and difference.

Among the other causes of headache are lesions of the brain, meninges and cerebral vessels; hydrocephalus, and disorders of cranial nerves and of the cerebrospinal fluid. In the group of cases due to such causes are found the greatest number of instances in which patients have unfortunately and wrongly had useless operations on sinuses. In cases of tumor of the brain pain is due to tension on the dura and is an early symptom. It is at first likely to be present only on arising in the morning or at some certain time of day. Later it becomes constant, persistent and severe and is of long duration, since most tumors develop slowly; it is worse at night. It may be general, unilateral, frontal or occipital, but the situation of the pain is not reliable for localization of the tumor. The associated symptoms help to distinguish it. These are: vomiting; abnormal eyegrounds; choked disk; unequal pupils; squint; disturbed reflexes; irregular, slow pulse; vertigo; drowsiness or insomnia; mental failure, and convulsions. Percussion of the skull may elicit tenderness and a changed note. These symptoms, when present, are an aid in localization. Tumors in the frontal region usually cause unilateral pain, as do growths in the occipital region. Cerebellar tumors more often cause diffuse pain. Tumors in the cerebellopontile angle are liable to cause pain referable to the fifth nerve, morning nausea, vomiting and vertigo.

Early abscess of the brain has a more acute onset; it causes generalized pain, along with fever, sweating and leukocytosis. Later the pain

becomes localized, grows worse and exists even in delirium. The pulse rate is slow and regular. Choked disk is not always present. There are periods without any symptoms in some cases, which is not true of tumors.

Lesions of the eye are among the most common causes of headache. Strain of the extrinsic muscles causes occipital headache, while strain of the intrinsic group causes frontal headache. An exception is when the superior oblique muscle is strained and causes pain in the frontal sinus by pulling on the trochlea. Ocular headache is worse during the afternoon and evening, after protracted use of the eyes. It may be felt only in the eyeball and may be a dull ache or intense throbbing, with nausea and dizziness.

Inflammation of the uveal tract causes severe pain similar to that due to irritation of the brain. There may be pain in the teeth, cheek or frontal bone. It is periodic and closely resembles neuralgia. Heterophoria and strabismus often cause severe pain in the orbit and the supra-orbital, temporal and occipital regions. There may be nausea and vomiting.

Intranasal pressure due to enlarged turbinates, vasomotor disturbances, deflected septum, growths, scar tissue and crusts can cause mild or severe frontal and occipital headache.

Pain due to conditions of the ear is unilateral. It may be of any intensity and either adjacent to the ear or in the entire side of the head. Pain in the ear may be referred from the sphenopalatine ganglion or the third division of the fifth nerve.

In syphilis the headache may be frontal, temporal or occipital, but is most often diffuse. It is a dull ache with pressure. It is persistent, deep, boring, periodic and nocturnal. The pain is often increased by moving the head. Dizziness, nausea and vomiting are common.

Migraine causes severe periodic pain which is unilateral. It recurs at irregular intervals over a long period of years, beginning at an early age. The pain begins on waking; it is sharp, boring and expansile and is in the eye, forehead, temple or entire side of the head. It increases in intensity until nausea and vomiting occur, bringing relief. It is found more often in women than in men and less frequently in older than in younger persons. It tends to be familial. Its cause is not always clear, but recent study points toward cerebral angiospasm. Sinus lesions, gastro-intestinal toxemia and other toxemias may play a part, since relieving these conditions often relieves migraine or what appears to be migraine.

Headache of gastro-intestinal origin is usually located in the frontal or temporal region. It is throbbing and is relieved by lying down and by purging. There is usually a history of gastric, hepatic or intestinal trouble. In cases of hepatic origin it is extremely persistent and severe.

Headache due to changes in the circulatory system may be due to anemia, in which case the pain is usually generalized, or may be of the constricting type.

Cerebral aneurysm causes pain that is throbbing and rhythmic.

The pain in arteriosclerosis and arterial hypertension is of the throbbing type and is in the temples or the entire head. It is frequently relieved by lying down and by purging.

Nephritic disorders most often cause frontal or occipital pain. This occurs in the morning, as in sinusitis, and is of varying degrees of severity. It is accompanied by drowsiness, dyspnea, nausea, vomiting, disturbance of vision, changes in the eyegrounds, edema, increased blood pressure and hematic and urinary changes.

Headache due to neuralgia or neuritis occurs at any time of the day or night and varies from one day to another as to location. It is usually due to some focus of infection.

As a rule, headache due to toxemia is irregular in onset and duration.

Endocrine dysfunction plays a part in headache that is often difficult to diagnose. In menstrual and climacteric disturbances, as well as in pregnancy, there is headache due to alteration of the ovaries, pituitary body and thyroid.

Thyroid disturbances do not cause characteristic headache. They are due to circulatory changes and to thyroid toxicosis. Stevens [3] stated that there is headache in certain patients at the menopause. It is usually frontal or parietal. There may be a dull type of pain that occurs three or four times a week or is continuous for longer periods. It is aggravated by fatigue and nervous tension. In many instances the patient is overweight and has a slow pulse rate, vertigo, a subnormal temperature, cold hands and feet and lowered metabolism. The condition is hypothyroidism, and the patient is benefited by thyroid extract.

Fishbaugh [4] reported cases of headache due to ovarian dysfunction, in which the patients were relieved by ovarian extract.

Headache of pituitary origin is often so severe as to be disabling. It is paroxysmal, persistent, boring, bitemporal and associated with drowsiness. It is characteristic that the pain usually can be stopped at once by lying down and begins again when the patient sits up. Ewing [5] stated that hyperplasia of the gland may be caused by alcoholism, nephritis, Parkinson's disease, arteriosclerosis and infectious diseases. This hyperplasia can cause varying degrees of headache. In women functional hyperplasia, usually of the anterior lobe, can cause severe

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3. Stevens, N. C.: The Thyroid and Headache at the Menopause, New England J. Med. **201**:168 (July 25) 1929.

4. Fishbaugh, E. C.: Headache in Relation to Ovarian Dysfunction, Endocrinology **11**:445 (Sept.-Oct.) 1927.

5. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1919, p. 905.

headache in the frontal region, through the temples and behind the eyes. It is present in the morning on waking and causes nausea. It may start at puberty or with the first pregnancy and may be present only at the time of the menstrual period or with each pregnancy. With succeeding pregnancies the pain becomes more intense and, according to Cushing, may even cause bitemporal hemianopia, owing to pressure on the optic commissure. The pain is due to an enlarged gland being confined in a sella turcica of normal size, thus causing intense pressure in the gland and the enveloping dura. It apparently is not due to hypersecretion, since administration of the whole gland frequently gives relief. Roentgen treatment of the gland gives marked relief in many cases of headache of pituitary origin.

During the past few years rhinologists have come to realize that allergic states can cause many types of headache. Undoubtedly they are the cause of many pains in the sinuses due to swelling of the lining membranes, and of frontal and occipital headache due to intranasal pressure. The patient may give a history of vasomotor rhinitis, urticaria, asthma or eczema.

Some of the more unusual causes of vague headache are worry and anxiety due to the stress of modern life, cervical rib and hydrocephalus. Nervous headache is likely to have an obscure cause, in many instances perhaps of endocrine origin.

Arthritis of the cervical spine has been recorded as a cause of headache. When the upper two or three vertebrae are involved the pain is referred to the occiput, but may reach the temporal and frontal areas. The pain also extends into the muscles of the neck. I have observed cases in which subacute, persistent nasopharyngitis caused a similar distribution of pain, with stiffness of the neck.

Headache is present in diabetes, probably due to the metabolites formed by faulty metabolism of carbohydrates and fats.

High altitudes, poisons, drugs and environmental conditions peculiar to various occupations account for a minor group of headaches.

Acute infections, such as meningitis, pneumonia, typhoid fever, influenza and the exanthems, are always accompanied by headache in the early stages.

Bearing in mind that these are but a few briefly described causes of headache, rhinologists may realize how careful they should be in assuming that any headache is due to trouble in their particular field. A careful taking of the history and thorough examination of other systems are necessary in order to solve the problem of etiology and relieve many patients whose most distressing symptom is most often headache.

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IMMUNIZATION OF THE UPPER RESPIRATORY TRACT

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The importance of the upper respiratory tract as a portal of entry for infectious agents is generally recognized, but information concerning the ways in which the agents induce local respiratory infection is meager and inconclusive. The frequent presence of pathogenic microorganisms in the nose and throat in the absence of actual disease indicates that these regions normally possess a considerable degree of resistance to the penetration of bacteria into the deeper tissues, and suggests the barrier action of mucus, cilia and epithelium. The conditions that tend to restrict the general spread of inflammatory agents throughout the body, however, are not so well understood, although the blood and lymphatic vessels, lymph nodules, macrophages, leukocytes and fluids of the tissues no doubt play an important part. In view of recent evidence indicating that antibodies in tissues may influence in large measure the immediate fixation of bacteria, perhaps more attention should be given to the localizing power of immune substances in the tissues of the upper respiratory tract. It is probable that under certain conditions antibodies may be formed locally,[1] and may remain there for some time in higher concentration than elsewhere in the body of the same animal. This occurs, presumably, when antigen is introduced into tissues in which macrophages have been mobilized by local specific or nonspecific stimulation. The localizing action of specific antibodies is apparently important in acquired immunity, as such tissues exhibit a definitely enhanced resistance to infection, due, in all probability, to the joint action of immune substances and phagocytic cells. The assumption seems warranted that mobilization of macrophages in the subepithelial tissues of the upper respiratory tract followed by the

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1. (*a*) Cannon, Paul R., and Sullivan, F. L.: Local Formation of Antibody by the Skin, Proc. Soc. Exper. Biol. & Med. **29**:517, 1932. (*b*) Walsh, T. E.; Sullivan, F. L., and Cannon, Paul R.: Local Formation of Antibody by the Nasal Mucosa, ibid. **29**:675, 1932. (*c*) McMaster, Philip D., and Hudack, Stephen S.: The Formation of Agglutinins Within the Lymph Nodes, ibid. **31**:751, 1934. (*d*) Hudack, Stephen S., and McMaster, Philip D.: Agglutinin Formation Withir the Lymph Nodes of Resistant and Susceptible Mice, ibid. **31**:753, 1934.

introduction of antigen into such tissues should furnish a more effective and persistent mechanism for the immediate and continued localization of bacteria of a similar antigenic nature.

In a preliminary report [1b] we presented some of the evidence on which we base our assumptions. We showed that the repeated instillation of a bacterial vaccine into the nostrils of rabbits was followed after a time by the appearance of agglutinins in the nasal mucosa. We stated that:

> If a local concentration of specific antibodies is a desirable condition in immunity, it may be obtained by the introduction locally, under suitable conditions, of the appropriate antigen. Such a reinforcement of a major portal of entry should strengthen significantly the resistance of these tissues to the entrance of pathogenic micro-organisms. To that extent the burden usually borne by the secondary general mechanisms of defence should be lessened.

The present article is an amplification and continuation of the experiments described in our preliminary report.

METHODS

Rabbits, from a source known to be free from snuffles, ranging in weight from 1,300 to 2,000 Gm., were used. Vaccines of Bacterium paratyphosum B and Bacterium typhosum were prepared by suspending the growth from a twenty-four hour agar slant in 5 cc. of a solution of 0.85 per cent saline to which solution of formaldehyde (1:333) had been added. This was done with the idea that such treatment causes less denaturization of the antigen complex than heat at 60 C. for one hour. These two types of micro-organisms were chosen merely because of the ease with which agglutinins can be demonstrated. The vaccine was instilled daily into the animal's nose by means of a medicine dropper, 12 drops being put into each nostril. At different intervals following varying periods of immunization the animals were killed, and the tissues immediately perfused through a cannula inserted into the thoracic aorta with an 0.85 per cent solution of sodium chloride, in order to make the organs and tissues as free from blood as possible. Weighed portions of the tissues, such as nasal mucosa, lung, liver, spleen, intestinal mucosa, stomach and kidney, were in most cases mixed with 15 parts by volume of a solution of equal parts of glycerin and salt solution, after which the tissues were ground in a mortar and allowed to extract at 37 C. for approximately seven days. In a few instances they were frozen in liquid nitrogen, crushed in a mortar surrounded by carbon dioxide snow and then extracted for twenty-four hours in salt solution. After the periods of extraction, the solutions were made up to a dilution for the original tissue of 1:120, were centrifugated until clear and were titrated at 37 C. against a living suspension of the bacteria. In a few instances agglutination at from 52 to 55 C. was also performed.

At various times during the experiments perfused tissues from normal rabbits were extracted and titrated against Bact. paratyphosum B and Bact. typhosum, in order to determine the presence or absence of nonspecific flocculating factors. This was necessary, because suspended materials, particularly in the emulsions of liver and skin, frequently interfered with the agglutination readings in the lower dilutions. This nonspecific flocculation was not usually present in extracts from nasal mucosa, lungs, spleen, kidney or blood serum. In none of the normal animals were

agglutinins demonstrable in a dilution of 1 : 120 or above. Prolonged centrifugation of the extracts of skin and liver, or agglutination at from 52 to 55 C., tended to eliminate the complicating nonspecific factor and to demonstrate the absence of a genuine agglutination of the micro-organism used. As a further control, three normal rabbits were given intranasal instillations of solution of formaldehyde (1 : 333) daily for ten days, and were killed eleven days later. Extracts of nasal mucosa, lungs, liver and spleen and serum at different dilutions, titrated as before, showed no agglutinins for Bact. paratyphosum B at 1 : 120 or above. It seems safe to conclude that under proper conditions the extracts of tissues of normal rabbits do not contain specific agglutinins for Bact. paratyphosum B, and that such extracts from immunized animals should reveal the presence and concentration of any specific agglutinins which might appear during the course of immunization.

OBSERVATIONS

Optimal Time Periods Before Extraction of Tissues; Influence of Numbers of Intranasal Instillations on Formation of Agglutinins After Intranasal Vaccination.—Our preliminary experiments were performed in order to determine whether agglutinins are demonstrable in the nasal tissues following the local instillation of a bacterial vaccine into the nostrils, regardless of their place of formation. We also wished to ascertain what conditions influence their appearance, such as the number and frequency of instillations required and the periods of time after instillation at which the tissues should be extracted, and to compare the concentration of antibody in the locally immunized tissues with that of the blood serum and other organs of the same animal. Twenty-five rabbits were used.

The general observations may be stated briefly as follows: 1. No agglutinins were demonstrable at a dilution of 1 : 120 or above in any tissues tested or in the blood serum in animals (five) given five intranasal instillations of the vaccine per day for two days and killed within ninety-six hours after the last vaccination. No titrations were done at lower dilutions. 2. The daily instillation of vaccine (sixteen animals) for from eight to thirteen days, followed by extraction of tissues from five to fifteen days after the last instillation, resulted in the ready demonstration of agglutinins in various tissues, invariably in higher concentration in the nasal mucosa, blood serum and occasionally the lungs than in the spleen, liver, stomach or intestine of the same animal. The agglutinin titers of the nasal mucosa ranged from 1 : 120 to 1 : 1,920; those of the blood serum were uniformly higher. The observations are recorded in table 1. 3. Intranasal vaccination for from six to eight days (four animals) with extraction of the tissues from two to four days after the last instillation yielded no agglutinins in two instances and only small quantities in two others (table 2).

These observations show that the continued application of a bacterial vaccine to the tissues of the upper respiratory tract may lead to the occurrence of a relatively high concentration of specific agglutinin in

such tissues, associated with a higher concentration in the blood serum. Although the latter observation makes it impossible to conclude whence the antibody arose, the lower concentration in such organs as the spleen, liver, stomach and intestines suggests that the antibody may have been formed principally in the tissues of the upper respiratory tract and thence diffused into the blood stream. Furthermore, the intensive application of the vaccine for two days, or the daily application for less

TABLE 1.—*Agglutinin Titers of Tissues and Blood Serum after Prolonged Intranasal Immunization Against Bact. Paratyphosum B*

Animal	Days of Vaccination	Interval Until Death	Blood Serum	Nasal Mucosa	Spleen	Lung	Liver	Stomach	Intestine
1*	11	12	1,920	960	120	960	480	—‡	—
2*	11	11	1,920	960	240	480	240	—	—
7	13	7	3,840	1,920	960	1,920	0	—	—
8	13	7	3,840	960	120	960	0	—	—
9	13	6	1,920	960	240	240	240	—	—
10	13	6	3,840	960	240	1,920	0	—	—
11	13	5	3,840	1,920	240	1,920	240	—	—
12	13	5	960	960	120	240	0	—	—
47*	9	14	3,840	960	960	480	960	—	—
48	9	15	1,920	480	120	240	960	—	—
68	9	11	1,920	480	—	240	—	0	0
65	9	11	1,920	480	—	120	—	0	0
66	9	12	960	240	—	0	—	0	0
67	9	12	960	0	—	0	—	0	0
51†	8	2	0	0	0	0	0	—	—
52†	8	4	960	240	0	120	0	—	—

* The animal was not perfused.
† Interval before extraction was much less than the optimal time.
‡ Not tested.

TABLE 2.—*Agglutinin Titers of Tissues and Blood Serum after Brief Intranasal Immunization Against B. Paratyphosum B*

Animal	Days of Vaccination	Days Until Death	Blood Serum	Nasal Mucosa	Spleen	Lung	Liver
49	6	2	240	120	120	240	0
50	6	3	0	0	0	0	0
51	8	3	0	0	0	0	0
52	8	4	960	240	0	120	0

than six days, seemed to be inadequate for the engendering of antibody in the nasal tissues. Finally, the optimal period of time before the extraction of tissues was from five to fifteen days after the last vaccination.

Consideration of these results suggests that the explanation may depend on the extent to which the repeated instillation of the vaccine stimulates the mobilization of macrophages in the subepithelial tissues of the upper respiratory tract. If one assumes that antibodies are formed principally by macrophages, there is little reason for a local formation of antibody until after such a mobilization. As will be described later, histologic examination demonstrated that such stimula-

tion actually results in the presence of increased numbers of macrophages beneath the epithelium of the nasal mucosa.

Influence of Previous Nonspecific Irritation of Nasal Mucosa on Local Presence of Agglutinins Following Intranasal Instillation of a Bacterial Vaccine.—Because of the probability that primary retention of antigen in the nasal tissues depends to a considerable extent on the number of macrophages available at the time of its instillation into the nostrils, experiments were performed in order to determine whether previous nonspecific stimulation favors the earlier appearance of antibody because of the more effective retention of antigen in the subepithelial tissues. Various irritants, such as solution of formaldehyde (1:333), undiluted ox bile, sterile sea sand and a vaccine of Staphylococcus albus, were

TABLE 3.—*Agglutinin Titers of Tissues and Blood Serum of Rabbits Immunized Intranasally Against Bact. Paratyphosum B Following Nonspecific Stimulation of Nasal Mucosa with Solution of Formaldehyde (1:333)*

Animal	Days of Formaldehyde	Days of Vaccination	Day of Death	Blood Serum	Nasal Mucosa	Spleen	Lung	Liver
25	1	4	4	120	480	0	0	0
26	1	4	4	240	480	0	0	0
27	1	4	5	240	480	0	0	0
28	1	4	5	0	0	0	0	0
29	1	4	6	0	0	0	0	0
30	1	4	6	480	240	0	240	0
62	1	4	5	480	0	0	0	0
63	1	5	6	960	240	120	480	0
41	3	7	4	120	240	0	240	0
40	3	8	4	480	240	0	0	0
39	3	8	4	480	120	0	0	0
38	3	9	4	960	960	0	240	0
37	3	9	4	960	240	0	0	120

instilled or blown into the nostrils of twenty-four rabbits, after which a vaccine of Bact. paratyphosum B was instilled into the nose daily for from four to ten days. The animals were killed from four to twelve days after the last vaccination, and the tissues extracted and titrated for agglutinins.

The results in this series (table 3) may be summarized as follows: 1. Six of eight animals treated with solution of formaldehyde for one day, followed after one day's rest by daily intranasal vaccinations for four days, with extraction of the tissues from four to six days after the last vaccination, yielded agglutinins in the nasal tissues or blood serum or both. In three of the animals only (25, 26 and 27) did the agglutinin titer of the nasal mucosa exceed that of the blood serum. 2. In five additional animals, treated daily with solution of formaldehyde for three days, followed by instillation of the vaccine for from seven to nine days, with extraction of the tissues on the fourth day after the last vaccination, the agglutinin titer of the nasal mucosa exceeded that

of the serum in but one instance. 3. The stimulation of the nasal tissues of eleven rabbits by such nonspecific irritants as a staphylococcic vaccine, ox bile or sea sand, followed by instillation of the paratyphoid vaccine, yielded no instance in which the agglutinin titer of the nasal mucosa exceeded that of the blood serum, although in all instances the titers of the nasal mucosa and lungs were higher than those of the spleen and liver.

These results emphasize the difficulty in demonstrating the exact site of the formation of antibody. This is not surprising when one recognizes the uncertainty regarding the general problem of the nature and origin of antibodies, and realizes that if antibody is formed in tissues its diffusion into the surrounding lymph and blood quickly leads to its detection in the blood serum. The fact, however, that at times the agglutinin titer of the locally immunized tissues was higher than that of the serum and invariably higher than that of several other organs

TABLE 4.—*Agglutinin Titers* of Tissues and Blood Serum of Rabbits Immunized Against Bact. Paratyphosum B by Subcutaneous Injection of Vaccine*

Animal	Blood Serum	Nasal Mucosa	Spleen	Lung	Liver
21	960	0	240	0	120
22	960	0	240	0	0
71	1,920	0	120	240	120
72	1,920	480	240	480	120

* Titrations were not taken above 1:1,920.

of the same animal is presumptive evidence at least of its local formation in the region in which the antigen was introduced. The possibility remains that the agglutinins demonstrable in the locally immunized tissue may have been formed elsewhere and have accumulated or become concentrated in the area of local immunization because of the hyperemia and irritation induced by the repeated local application of the bacterial vaccine. In recent articles on the formation of antibodies by lymph nodes, McMaster [1c] and Hudack [1d] argued against this possibility.

Influence of General Immunization on the Concentration of Agglutinins in Nasal and Other Tissues.—In the further consideration of the source of the antibody in the tissues, particularly with reference to the possibility of a local accumulation or concentration as the result of specific or nonspecific stimulation, animals were immunized subcutaneously in order to secure a relatively high titer of agglutinin in the blood serum. The animals were then killed, and the agglutinin titers of the nasal tissues, spleen, liver and lung compared with those of the blood serum. The results are shown in table 4.

Variations in agglutinin titers of the different tissues may be explained in part by the incompleteness of perfusion; nevertheless,

these experiments demonstrate clearly that antibodies may be present in relatively high concentration in the blood serum and yet not be demonstrable in the nasal mucosa at a dilution of 1 : 120, showing, therefore, that antibodies may be unequally distributed throughout the organs and tissues.

Another group of six animals was similarly immunized, following which solution of formaldehyde (1 : 333) was instilled into the nose for two or three days to simulate the irritation present in the locally immunized rabbits. The results are given in table 5.

It is evident from these findings that nasal irritation by solution of formaldehyde may have no effect in increasing the concentration of agglutinins in the nasal tissues, despite the relatively high titer of the blood serum. Unfortunately, the titrations of blood serum were not carried to a higher dilution than 1 : 1,920, so no definite conclusion

TABLE 5.—*Agglutinin Titers* of Tissues and Blood Serum of Rabbits Immunized Against Bact. Paratyphosum B by Subcutaneous Injection of Vaccine, in Which Nasal Mucosa Was Irritated by Introduction of Solution of Formaldehyde (1:333)*

Animal	Blood Serum	Nasal Mucosa	Spleen	Lung	Liver
23	960	0	120	0	0
24	1,920	0	960	120	0
53	1,920	480	120	120	120
54	1,920	120	240	120	0
69	1,920	480	480	960	0
70	1,920	480	240	240	0

* Titrations were not taken above 1:1,920.

can be drawn as to what extent the nasal irritation favored the local accumulation in the nasal tissues of the antibody in the blood. But it can be seen in animals 23 and 24 that it is possible for the local irritation to have no effect in increasing the concentration of agglutinins, despite the relatively high titer of the blood serum.

A final series of animals was immunized intranasally with a vaccine prepared from Bact. typhosum, in order to determine the specificity of the immune reaction to Bact. paratyphosum B. The vaccine was instilled eleven times in thirteen days, and the animals were killed from seven to nine days after the last vaccination. In this series the extracts of nasal tissues were titrated against both Bact. typhosum and Bact. paratyphosum B. The results are shown in table 6.

Here it is seen that no agglutinins for Bact. paratyphosum B were demonstrable in the extracts of nasal tissue of any animal at a dilution of 1 : 120 or above, whereas agglutinins to a titer of from 1 : 240 to 1 : 960 were present against the homologous Bact. typhosum. Furthermore, agglutinins for Bact. typhosum were always in higher concentration in extracts of nasal tissues than in those from the skin, kidney or

testis of the same animal. In two animals, however, the titer of the extract of lung equaled that of the nasal mucosa. In all instances the titer of the blood serum was higher than that of extracts of nasal tissues or lungs. One may conclude, therefore, that the agglutinins formed in these animals were specific for the homologous microorganism, and were usually present in higher concentration in the locally immunized region than in the skin, testis and kidney. The findings also suggest the possibility that in some animals agglutinins may have been formed in the lungs; this may occur following the aspiration of antigen into the lungs. It is well known that oils, as in the intranasal administration of antiseptics in oils to infants, may reach the lungs and there be engulfed by septal cells.[2]

We made a few observations along similar lines, viz., by dropping a 1 per cent solution of trypan blue into the nostrils of rabbits, killing the animals a few hours later and observing the distribution of the

TABLE 6.—*Agglutinin Titers of Tissues and Blood Serum of Rabbits Immunized Against Bact. Typhosum by Intranasal Vaccination; Results of Titration of Nasal Tissue Extracts Against Bact. Paratyphosum B*

			Nasal Mucosa					
Animal	Day Killed	Blood Serum	B. Typhosum	B. Paratyphosum B	Kidney	Testis	Skin	Lung
80	7	3,840	960	0	240	0	240	—
81	7	1,920	240	0	0	0	0	240
82	8	3,840	960	0	240	—	120	480
83	9	3,840	960	0	0	—	120	960

dye. The results in the earlier experiments were somewhat equivocal, because too much dye was used, but the distribution was of interest. The lungs became diffusely blue, and mucus in the trachea was blue. The anterior cervical lymph nodes were also stained, but the peritracheal lymphatics were uncolored. Although these effects suggested that the dye reached the lungs directly rather than through the blood or peritracheal lymphatics, a more crucial type of experiment was performed to secure additional information. Two rabbits were prepared as follows: Under local anesthesia a tracheotomy was performed, a glass tube was inserted into the lower portion of the trachea, and the upper portion was packed with absorbent cotton. A solution of trypan blue was dropped into the nostrils of one animal, which was left in its cage for five hours before being killed by an air embolus. Although so much

2. Pinkerton, Henry: Oils and Fats: Their Entrance into and Fate in the Lungs of Infants and Children; A Clinical and Pathologic Report, Am. J. Dis. Child. **33**:259 (Feb.) 1927. Laughlen, G. E.: Studies on Pneumonia Following Nasopharyngeal Injections of Oil, Am. J. Path. **1**:407, 1925. Corper, H. J., and F. Harold: The Intratracheal Injection of Oils for Diagnostic and Therapeutic Purposes, J. A. M. A. **79**:1739 (Nov. 18) 1922.

dye was instilled that the subcutaneous tissues, liver and kidneys became distinctly blue, the lungs were only faintly stained. The tracheal pack and the trachea above it were dark blue. In the second animal, only 4 or 5 drops of dye solution was placed in each nostril, and the animal was killed three hours later. The lungs were entirely unstained. The trachea below the cotton pack was white, as was also the lower half of the pack. The upper half of the pack, however, was dark blue, and

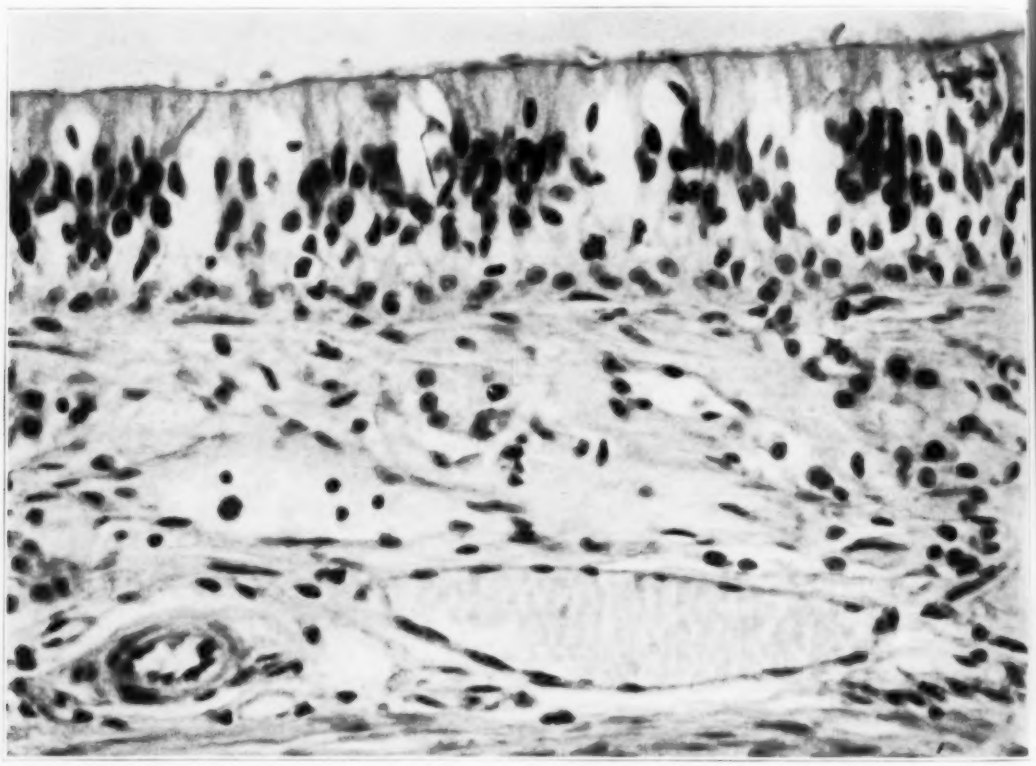

Fig. 1.—Photomicrograph of the nasal mucous membrane of a normal rabbit. Note the relative scarcity of macrophages and lymphoid cells in the subepithelial tissues; reduced from a magnification of × 600.

the mucous membranes of the mouth, pharynx and upper part of the esophagus were similarly stained.

These experiments showed clearly that if the trachea is obstructed from within, a solution of trypan blue introduced into the nose does not enter the lungs except as minimal amounts are absorbed from the blood stream. It is evident, then, that material in solution can flow down the upper respiratory tract and enter the lungs directly. This

suggests that a bacterial suspension instilled into the nostrils may, similarly, reach the lungs by way of the trachea, and may there be retained and metabolized by the septal cells, with the possible formation of antibody. Such a series of events, if true, would serve to explain our findings of relative high agglutinin titers of the extracts of lung in some of the animals vaccinated intranasally.

Because of statements in the earlier literature that bacteria introduced into the nasal passages may be recovered relatively quickly from

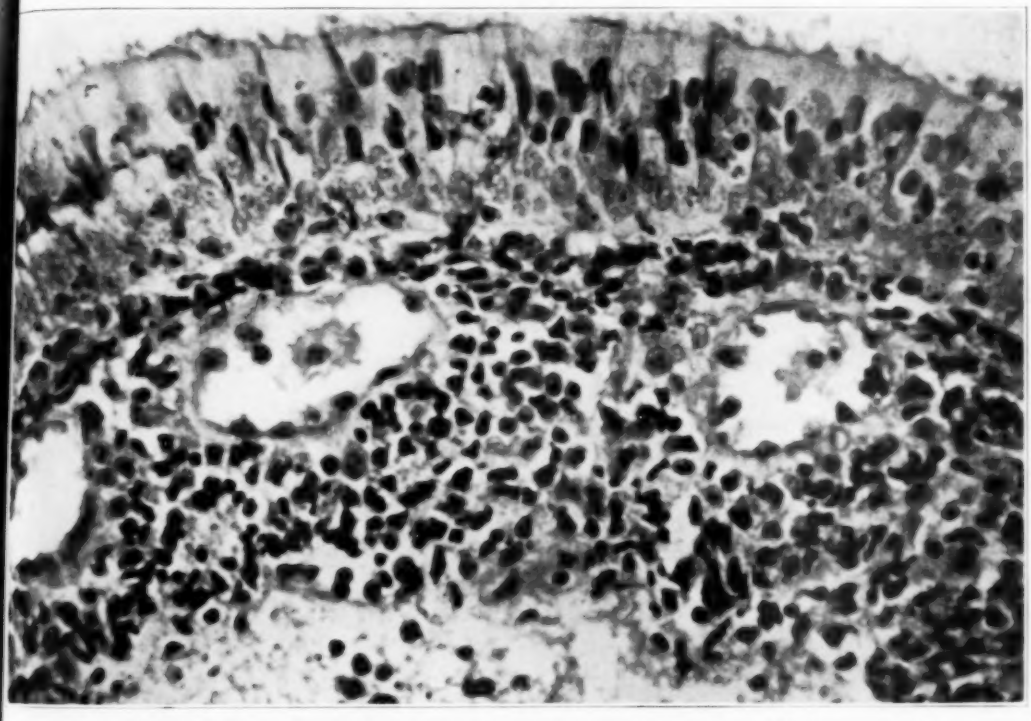

Fig. 2.—Photomicrograph of the nasal mucous membrane of a rabbit immunized intranasally with a vaccine of Bact. paratyphosum B. Note the dense accumulation of macrophages and lymphoid cells in the subepithelial tissues; reduced from a magnification of × 600.

the blood stream, a few experiments were performed to determine to what extent this might be true. Twelve drops per nostril of a living suspension of Bact. paratyphosum B or Staph. albus was instilled in three rabbits, and cardiac blood cultures made at intervals up to seventy-five minutes afterward. In no instance were bacteria demonstrable in the blood stream. Three more animals were treated similarly, except that undiluted ox bile was instilled intranasally into one rabbit three

hours before the living bacteria were placed in the nostrils; in a second animal, epinephrine was placed in the nostrils forty minutes before the bacteria were introduced, and a third animal was kept in the refrigerator for forty-five minutes before the bacteria were instilled. Despite these procedures no bacteria were demonstrable in the blood cultures in the succeeding seventy-five minutes after the intranasal application of the living bacteria. It is apparent from these experiments that living bacteria of these types do not readily penetrate the epithelial barrier of the nasal mucosa.

Histologic Changes Produced in Nasal Tissues Following Repeated Intranasal Instillation of Bacterial Vaccine.—Histologic preparations from various areas of the upper respiratory tract of normal rabbits and of rabbits immunized locally with bacterial vaccines showed changes which agree essentially with those described by Linton.[3] In sections from the rabbits immunized locally there was a marked increase of cells of inflammation beneath the epithelium, particularly macrophages, lymphocytes, mononuclear cells and polymorphonuclear leukocytes. The lymphoid nodules of the anterior nasopharynx were hyperplastic, and at times showed germinal or reaction centers. The mucous glands were obviously more active than in the normal animal. In other words, increased numbers of macrophages or potential macrophages were present in the tissues through which particles which might penetrate the epithelium must pass in order to reach the lymphatic or blood vessels. The lymphoid hyperplasia suggested also that even if particles should enter the lymphatic system they might not pass the areas of increased lymphoid activity along the paths of lymph drainage. Figures 1 and 2 illustrate the histologic differences between normal rabbits and rabbits immunized intranasally.

COMMENT

The experiments demonstrate that the intranasal application of certain bacterial vaccines produces both an increased concentration of specific antibody in the nasal tissues and a mobilization of leukocytes and macrophages in the subepithelial areas, conditions which elsewhere in the body have been shown to be associated with an increased resistance to infection.[4] Linton [3] demonstrated that this is also true for the upper respiratory tract. He instilled a suspension of a highly virulent strepto-

3. Linton, C. S.: Resistance of the Upper Respiratory Mucosa to Infection, Ann. Otol., Rhin. & Laryng. **42**:64, 1933.

4. (*a*) Gay, F. P.: Local or Tissue Immunity, Arch. Path. **1**:590 (April) 1926. (*b*) Cannon, Paul R., and Pacheco, G. A.: Studies in Tissue Immunity: Cellular Reactions of the Skin of the Guinea Pig as Influenced by Local Active Immunization, Am. J. Path. **6**:749, 1930. (*c*) Pacheco, G. A.: Local Tissue Immunity, Arch. Path. **13**:868 (June) 1932.

coccus into the nostrils of normal rabbits and guinea-pigs and induced a severe infection of the nasopharynx which was frequently fatal, whereas similar instillations into animals previously vaccinated intranasally with a heat-killed vaccine of the streptococcus led to distinctly milder infections.[4d] He showed that such an intranasal vaccination caused the accumulation of large numbers of leukocytes, macrophages and lymphocytes in the subepithelial tissues of the nasopharynx. Although he did not examine the nasal tissues of the vaccinated rabbits for antibody, it is not improbable, in view of our observations, that an increased amount was present.

The rôle of antibody in tissues has aroused considerable interest in recent years, particularly because of the work of Opie [5] on the significance of the Arthus reaction, and that of Rich [6] on the relationship of allergy to resistance. Opie assumed that the localizing inflammation of the Arthus reaction resulted from the union in the tissues of antigen and antibody, although he attributed the source of the antibody to the blood. Rich and his associates emphasized the importance of antibodies in immune tissues, because of their observations that bacteria tended to adhere to such tissues and to one another by an agglutinative process which restricted the free "drift" of the micro-organisms and in that way diminished the chance of generalization. Rich concluded that the immediate localizing mechanism was an antigen-antibody reaction entirely independent of the later manifestations of inflammation. Cannon and Pacheco [4b] made similar observations in their studies of the immunity of tissue in staphylococcic infections, but emphasized the action of flocculating and opsonizing antibodies and the accumulation of phagocytes in favoring not only the immediate, but also the continued, localization of the infectious agents near the site of introduction. If the assumption is valid that immunization insures the more effective retention of invading bacteria at or near the portal of entry, the combination of conditions which makes this localization most certain should be secured. If small amounts of antibody in tissue and only a few phagocytes can restrict the spreading of bacteria through the sur-

4d. Bull and McKee (Bull, C. G., and McKee, C. M.: Respiratory Immunity in Rabbits, Am. J. Hyg. **9**:490 [July] 1929), in similar experiments on rabbits, found that animals immunized locally by the introduction of pneumococcus vaccine into the nose were remarkably more resistant to infection when the same variety of living pneumococcus was dropped into the nares than were normal animals, in spite of the fact that no agglutinins were demonstrable in the blood serum when the infecting dose was given.

5. Opie, Eugene: Inflammation and Immunity, J. Immunol. **17**:329, 1929.

6. Rich, Arnold Rice: The Demonstration that Allergic Inflammation Is Not Necessary for the Operation of Required Immunity, Proc. Nat. Acad. Sc. **16**:460, 1930; The Mechanism Responsible for the Spread of Bacteria in the Immune Body, Bull. Johns Hopkins Hosp. **52**:203, 1933.

rounding tissues, larger amounts of specific antibody and greater numbers of phagocytic cells should reenforce the defensive mechanism. This is precisely the purpose of local immunization.

In the upper respiratory tract the mesenchymal cells of the subepithelial tissues act, presumably, to impede the dissemination of bacteria which have penetrated the epithelial barrier. Such cells, under normal conditions, are not numerous, and the varying levels of cellular resistance depend to a considerable degree on the types and numbers of cells which accumulate from the blood stream. Local irritation of the nasal passages, as by a bacterial vaccine frequently applied, leads to the accumulation in the subepithelial tissues of leukocytes and macrophages and to hyperplasia of the lymphoid tissues, particularly those of the nasopharynx. This mobilization of macrophages furnishes, in all probability, an added cellular factor of safety in the event that pathogenic bacteria penetrate the nasal mucosa. The unreliability of such a factor alone is suggested by the experiments of Clark.[7] She observed that although increased numbers of phagocytic cells enhance the resistance of the pleural cavity of the rabbit to infection with a streptococcus, this is not true in the case of the pneumococcus, in which the addition of specific antibody is necessary for the acquisition of a satisfactory immunity. Despite the ineffectiveness of phagocytic cells for certain types of micro-organisms, it is nevertheless probable that simple mobilization of such cells may elevate the level of resistance to the point at which they may dispose of many types of bacteria more quickly and more effectively.

Probably of more importance than the mobilization of phagocytic cells, at least for the early fixation of the antigenic particles, is the presence of specific antibody in the tissues. Rich and McKee [8] showed that the immediate fixation of pneumococci in passively immunized rabbits occurs in the absence of inflammation or any evidence of mechanical obstruction of lymphatics or deposition of fibrin, as described by Menkin [9] in other types of inflammation. Later, however, and especially in the more intense inflammations, such factors may aid considerably in restricting the dissemination of the infectious agents. Ultimately, also, the disposal of the localized bacteria probably depends to a large extent on the ability of the phagocytes to engulf and destroy the bacteria, as there is but meager evidence that, in vivo, extracellular bactericidal agencies play a significant part in the destruction of the micro-organisms.

7. Clark, Ada R.: The Rôle of Clasmatocytes in Protection Against the Pneumococcus, Arch. Path. **8**:464 (Sept.) 1929.

8. Rich, Arnold R., and McKee, Clara M.: The Protective Action of Antibody in Immunized Animals Deprived of Leukocytes, Arch. Path. **14**:284 (Aug.) 1932

9. Menkin, Valy: An Aspect of Inflammation in Relation to Immunity, Arch. Path. **12**:802 (Nov.) 1931.

Not only the presence of specific antibody but also its concentration must be considered, and it is probable that local immunization may provide a more effective way of increasing the concentration of antibodies in tissues threatened with infection. Our experiments demonstrated that local intranasal immunization is associated with a higher concentration of specific agglutinins in the nasal tissues than in the other organs of the same animal, and even at times higher than in the blood serum. Furthermore, the agglutinin titers of extracts of nasal tissues of animals immunized intranasally are in most cases higher than those of animals immunized subcutaneously and showing a high titer in the blood serum. We suggest, therefore, that intranasal immunization may lead to the local formation of antibodies in the subepithelial nasal tissues, whence they may gradually diffuse into the lymphatic vessels and then reach the blood stream. We do not doubt that general formation of antibodies also occurs, in view of the probability that in the earlier stages of immunization some of the bacterial particles escape into the blood stream. But with each succeeding instillation of the vaccine it is likely that more bacteria are retained and metabolized by the macrophages, with an increasing local formation of antibody.

Complete proof of this strictly local formation is admittedly difficult. As mentioned before, any bacteria which escape into the blood early in the process of local immunization will engender antibody which may then tend to obscure the difference in titer between serum and locally immunized tissues. Furthermore, locally formed antibody probably diffuses rather quickly into the lymph and blood, thus making it difficult to tell from which source it arose. The experiments of Freund [10] and of Freund and Whitney [11] support this view. They demonstrated that agglutinins in organs and tissues are readily removed by perfusion, and evidently are loosely attached, if at all, to the cells. They concluded that even in the so-called perfusion-fast skin and uterus the agglutinins persisted, not because of their attachment to the cells, but because of the inaccessibility to the perfusion fluid. If these assumptions are correct, the antibodies are not retained locally for any length of time, and the only proof possible of the strictly local formation of antibodies would depend on their demonstration locally before they can be found in other organs or fluids. Uncertainty as to the exact time at which to extract the tissues in order to detect the earliest traces of antibody makes proof of their definite origin exceedingly difficult. Our observa-

10. Freund, Jules: Distribution of Immune Agglutinins in the Serum and Organs of Rabbits, J. Immunol. **14**:101, 1927.

11. Freund, Jules, and Whitney, Caroline E.: The Distribution of Antibodies in the Serum and Organs of Rabbits: II. The Effect of Perfusion upon the Antibody Content of Serum and Organs, J. Immunol. **15**:369, 1928.

tions, nevertheless, offer some evidence for the local origin of antibodies for the following reasons: 1. The local concentration of antibodies in the nasal tissues is demonstrable only after the repeated instillation of vaccine, usually from nine to twelve days. This delayed response may be explained by the assumption that a certain amount of stimulation is required for an adequate mobilization of macrophages in the subepithelial tissues, and until this occurs, antibody will not be detectable. With repeated local vaccination, however, sufficient numbers of macrophages are finally mobilized to capture the particles of vaccine entering the subepithelial tissues, thus engendering the local formation of antibody at an accelerated rate. 2. Nonspecific irritation of the nasal passages in animals subcutaneously immunized does not lead to a concentration of agglutinin in the nasal tissues comparable in amount to that obtainable by continued local immunization, despite the presence of a relatively high agglutinin content of the blood serum of the same animal. 3. Local intranasal vaccination at times is associated with a higher concentration of agglutinin in the nasal tissues than in the blood serum of the same animal.

Although the vaccine must pass the epithelial barrier of the nose and pharynx, our observations do not show how this happens. It is evidently a slow process, as shown by our failure to recover microorganisms from the blood stream within an hour, approximately, after the intranasal instillation of suspensions of living organisms. MacMahon [12] submitted evidence that particles of carbon do not penetrate the nasal epithelium, whether intact or broken, and that the epithelial cells are not phagocytic for these particles. Linton suggested that bacterial products, by decreasing ciliary action or viscosity of the mucus or by causing a stagnation of mucus, may favor the penetration of bacteria into the epithelium. More work is necessary to determine which factors are operative. The evidence, at any rate, indicates that the particles of vaccine, in some way, pass the epithelial barriers, with a resulting formation or accumulation of specific antibody in the nasal tissues. Regardless of whether the antibody is formed locally or accumulates locally, the results suggest that the local antigenic stimulation of an important portal of entry, by mobilizing both antibody and phagocytic cells, should enhance materially the resistance of such tissues to antigenically similar infectious agents.

SUMMARY AND CONCLUSIONS

An experimental study of the problem of active immunization of the upper respiratory tract of rabbits was made with the object of

12. MacMahon, Bernard J.: The Spread and Phagocytosis of Particulate Matter in Nasal Mucous Membrane of the Rabbit, Ann. Otol., Rhin. & Laryng. **42**:660, 1933.

determining the effects of local immunization on the development of antibodies at the site of immunization and elsewhere. Vaccines of Bact. paratyphosum B and Bact. typhosum were injected subcutaneously or instilled into the nostrils, and the agglutinin content of various organs and tissues compared with that of the blood serum and nasal mucosa of the same animal. An effort was made to determine which conditions, such as local irritation or nonspecific inflammation, might influence the passage of bacteria through the epithelium of the nose and pharynx and whether dye solutions or bacterial vaccines instilled into the nostrils can reach the lungs directly through the trachea. Histologic examinations of the tissues of the upper respiratory tracts of normal and locally immunized animals were made in order to ascertain what cellular changes may be produced by such procedures. The results may be summarized as follows:

1. The repeated intranasal instillation of vaccines of Bact. paratyphosum B or Bact. typhosum caused the development of specific agglutinins in the various organs and in the blood of the immunized animal. Simultaneous titration of different tissues of a perfused animal revealed the agglutinin content of the nasal tissues usually higher than that of all other organs tested, but lower than that of the blood serum. Agglutinins in the nasal tissues were demonstrable in fairly high dilution only after the intranasal instillation of the vaccine for at least six days, the highest titers being in animals treated daily for from nine to thirteen days with extraction and titration of the tissues from five to seven days after the last vaccination.

2. The repeated intranasal application of these vaccines caused structural changes in the subepithelial tissues, with an accumulation of leukocytes, macrophages and mononuclear cells and hyperplasia of the lymphoid tissues.

3. The agglutinin content of the nasal tissues in a few instances was higher than that of the blood serum of other tissues of the same animal, suggesting that the antibody was formed locally in the region of vaccination.

4. Nonspecific stimulation of the nasal tissues of rabbits immunized subcutaneously and with a high agglutinin titer of the blood serum did not lead to as high agglutinin titers of the extracted nasal tissues as was usually the case after intranasal vaccination.

5. Living bacteria instilled into the nostrils did not enter the blood stream in detectable numbers within an hour, demonstrating the barrier action of nasal and nasopharyngeal epithelium. A solution of trypan blue instilled into the nostrils entered the lungs directly by way of the trachea.

6. The experiments support the notion that local intranasal vaccination may lead to local concentration of specific agglutinins in the

nasal tissues and mobilization of leukocytes and macrophages in the subepithelial tissues of the upper respiratory tract. They also furnish evidence for the view that these agglutinins are, at least in part, formed locally. Complete proof of this point is still lacking. The conclusion is drawn that local immunization by mobilizing macrophages and by favoring the formation or concentration of specific antibody in the region of vaccination should enhance the resistance of such tissues against similar living bacteria. The reasons for such a conclusion are discussed.

THE PERITONSILLAR SPACES

AN ANATOMIC STUDY

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The ease with which the large majority of normal tonsils can be displaced from their normal position, either by traction of the tonsil itself or by pressure on the anterior faucial pillar, is a matter of every-day observation to those performing operations on the tonsils. This dislocation of the tonsil is so important to the technic of all tonsillectomies that a firmly fixed tonsil makes any type of operation much more difficult. With this dislocation there must, of course, be some disturbance of the normal anatomic relations, and the study to be outlined in this paper was conceived with the idea of determining, if possible, just what this disturbance is. Is the region external to the dislocated tonsil filled in by an internal bulging of the superior constrictor muscle, or is there sufficient elasticity in the areolar tissues of the tonsillar fossa to permit the approximation of the faucial pillars outside of the tonsillar capsule?

In addition to the data that were obtained relative to this question, certain rather interesting relations of the peritonsillar spaces were demonstrated.

This work was done through the courtesy of Professor Batson in the anatomic laboratories of the Graduate School of Medicine of the University of Pennsylvania. The material used for making the injections was a solution that was suggested by Dr. Valentine Miller in his work on laryngeal edema, and consisted of a 10 per cent solution of gelatin stained with *Wasserblau*. The gelatin was injected while warm and fluid. It solidified on cooling making its subsequent position and relations easily determined. Dr. Miller gave technical suggestions and aid in the work.

As it was practically impossible to obtain fresh adult bodies, cadavers were used that had been preserved for the anatomic laboratory. It was, of course, realized that there would be a distinct diminution in the elasticity of the tissues which would probably tend to cause the injected material to escape into and through the natural spaces instead of changing the relation of the structures to each other. However, the only practical difference was that less fluid could be injected without the danger of rupturing the tissue, and the distention of the faucial structures was not so marked as it would have been in a fresh or living subject.

The fresh bodies of infants were available, but it was practically impossible to insert the needle into the peritonsillar space, whereas in the adult there was no difficulty in making injections into the tonsillar fossa whenever it was desired.

In regard to the question of tonsillar dislocation, I found that the tonsil was readily separated from the superior constrictor muscle by the substance injected into the tonsillar fossa. This seems to prove that there were no firm attachments between the superior constrictor muscle and the tonsillar capsule, and that the space of the peritonsillar areolar tissue was probably filled in by an approximation of the anterior and

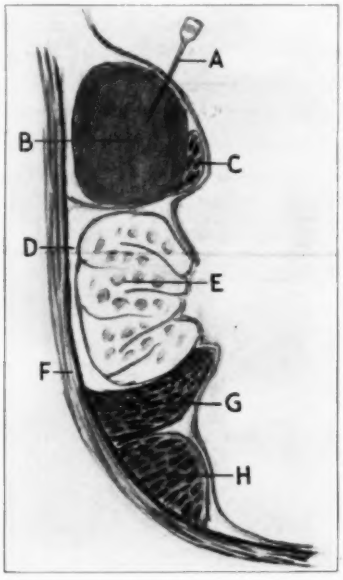

Fig. 1.—The needle (*A*) is inserted just under the mucosa in front of the palatoglossus muscle *(C)*. The gelatin mass *(B)* does not pass back into the tonsillar fossa *(D)* but bulges forward toward the mouth. *E* indicates the tonsil; *F*, the superior constrictor muscle; *G*, the palatopharyngeus muscle, and *H*, the salpingopharyngeus muscle.

posterior pillars when the tonsil was dislocated toward the median line. On the other hand, there was evidence of a fairly firm attachment between the sheath of the palatopharyngeus muscle and the posterior surface of the tonsillar capsule.

Another important finding was the demonstration of certain barriers to the extension of the injected material and the fact that these barriers practically all run in a longitudinal direction, following more or less closely the arrangement of the faucial musculature. The solution of gelatin traveled readily upward and downward but was definitely limited

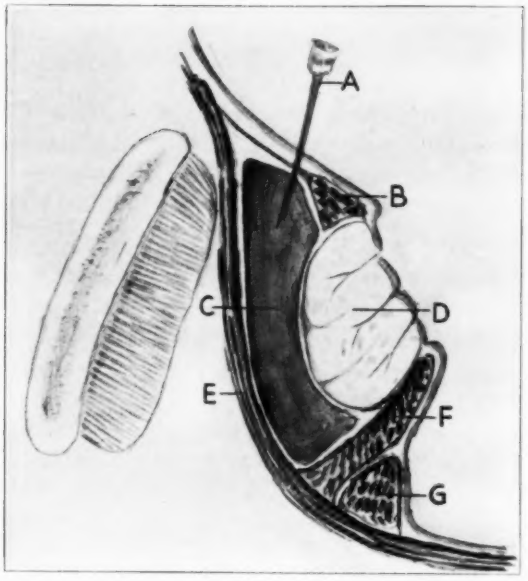

Fig. 2.—The position of the gelatin mass *(C)* when the injection is made into the tonsillar fossa through the anterior pillar. The tonsil *(D)* is readily separated from the superior constrictor muscle *(E)* but not from the palatopharyngeus muscle *(F)*. The tonsillar fossa can be readily reached by inserting the needle *(A)* through the mucous membrane external to the palatoglossal muscle *(B)*, as shown in this diagram, or by inserting the needle between the palatoglossus muscle and the tonsillar capsule. The location of the gelatin mass is the same following either method of injection. *G* indicates the salpingopharyngeus muscle.

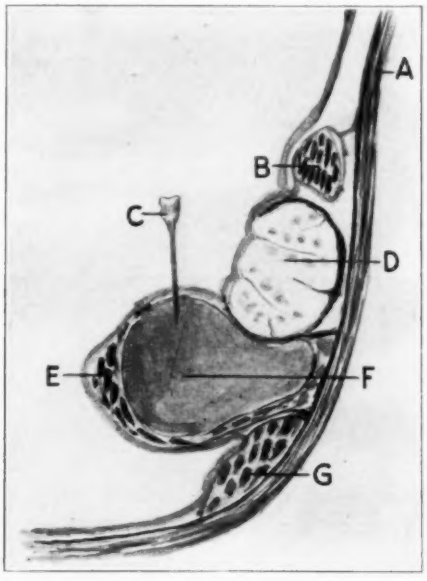

Fig. 3.—The needle *(C)* was inserted just under the mucous membrane of the posterior pillar. The gelatin mass *(F)* occupies the posterior pillar, coming in contact with the posterior surface of the tonsil *(D)*, but does not spread into the tonsillar fossa or posteriorly into the lateral wall of the pharynx. *A* indicates the superior constrictor muscle; *B*, the palatoglossus muscle; *E*, the palatopharyngeus muscle, and *G*, the salpingopharyngeus muscle.

in its forward or backward extension. When it was injected just under the mucosa of the anterior pillar, it extended forward and upward but not posteriorly. When it was injected between the superior constrictor muscle and the capsule of the tonsil (the tonsillar fossa), it only extended anteriorly to the region of the palatoglossus muscle and posteriorly to the palatopharyngeus muscle. Its extension upward into the soft palate was limited by the edge of the hard palate, but downward along the pharyngeal wall toward the pyriform fossa its progress was limited only by the amount of fluid injected. When put just under the mucosa of the posterior pillar, it spread upward on the posterior surface

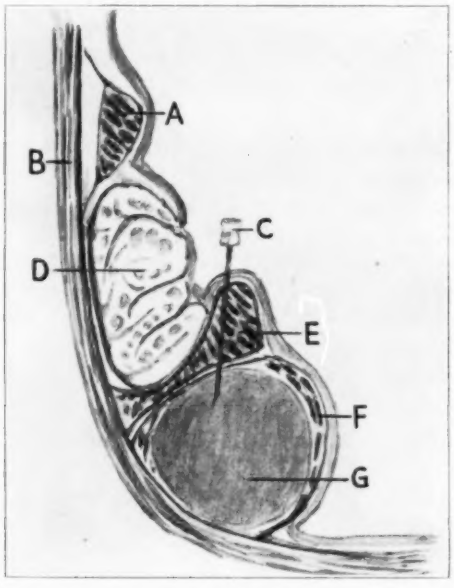

Fig. 4.—The needle *(C)* is inserted through the posterior pillar into the lateral wall of the pharynx. The gelatin mass *(G)* occupies the lateral wall of the pharynx back of the posterior pillar. The mass does not enter the posterior pillar or the posterior pharyngeal wall and is not in intimate contact with the capsule of the tonsil *(D)*. *(A)* indicates the palatoglossus muscle; *B*, the superior constrictor muscle; *E*, the palatopharyngeus muscle, and *F*, the salpingopharyngeus muscle.

of the palate almost to the eustachian tube, but not anteriorly or posteriorly. When the needle was pushed through the posterior pillar into the lateral pharyngeal wall, the gelatin extended upward in the pharyngeal wall almost to the fossa of Rosenmüller and downward to the level of the epiglottis but did not invade the posterior wall or the posterior pillar. This seems to indicate that there are definite longitudinal attachments of the mucosa to the pharyngeal wall, probably in

connection with the sheath of the salpingopharyngeus muscle and again between the salpingopharyngeus and the palatopharyngeus muscles. The palatopharyngeus muscle acts as a barrier to the posterior extension of fluid injected into the tonsillar fossa. The attachment of this muscle to the posterior surface of the capsule of the tonsil prevents the injected mass from reaching the posterior surface of the tonsil. In a similar manner, the palatoglossus muscle and its sheath act as a barrier to the posterior extension of fluid injected immediately under the mucous membrane of the anterior pillar.

I hesitate to make an estimation of the clinical importance of these anatomic findings, though the spread of suppurative conditions inside of the superior constrictor muscle seems to occur in the same planes as the gelatin mass followed in these anatomic injections. When a suppurative process begins in the tonsillar fossa (peritonsillar abscess), it extends upward into the palate but does not invade the posterior pillar or the posterior pharyngeal wall. If, however, the infection starts in the posterior pillar (peritonsillar abscess in the posterior position), the tonsillar fossa and the lateral pharyngeal wall are not involved. This is true in the majority of cases, though one must recognize that suppuration is not always limited by a fascial barrier.

Another possible clinical application concerns the method of injection of a local anesthetic for tonsillectomy. For instance, if a needle is inserted through the plica into the tonsillar fossa, one injection would probably anesthetize the operative area more or less completely, as the tonsillar branch of the glossopharyngeal nerve comes through the superior constrictor muscle and is the main sensory nerve to the tonsil. However, to be sure of anesthetization of the posterior pillar another injection into the posterior pillar itself would be necessary.

ROENTGENOLOGIC EXAMINATION OF THE MAXILLARY SINUS BEFORE AND AFTER OPERATION

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This paper represents a study of maxillary sinusitis from a roentgenologic standpoint with the aid of iodized oil. Twelve cases have been studied. Each one of the patients had chronic disease of the maxillary sinus in which the radical operation on the antrum was indicated but in which the intranasal operation was done for varying reasons. Some of the patients could not afford the time and expenses of hospitalization and operation; some refused an external operation, and because of striking results seen in two cases I advised some of these patients to have the intranasal operation when the radical one was indicated. Two patients were used as controls. Both of them had bilateral disease of the antrum, and one side was operated on by the Caldwell-Luc method and the other by the intranasal route.

X-ray views, anteroposterior and lateral, were taken after the injection of iodized poppy-seed oil 40 per cent into the antrum for diagnosis. Each antrum was examined separately.

The postoperative pictures were taken under the same conditions except that it was necessary to block the window. This was accomplished by means of a rubber bag or petrolatum-treated gauze packed under the inferior turbinate.

The operative procedure was confined to pushing the inferior turbinate toward the septum and making a window as large as possible in the inferior meatus without attempting to remove any of the antral mucosa.

All but two of the patients had been under my care for long periods previous to operation. Irrigations followed by instillation of various germicidal agents were employed as a routine treatment. The postoperative care was given over a considerable time, as it was desirable to keep the patients under observation and because more postoperative care is necessary after an intranasal operation than is usually required after the Caldwell-Luc procedure.

Of the twelve patients six are well from a clinical and from a roentgenologic standpoint. This means that the symptoms have disappeared,

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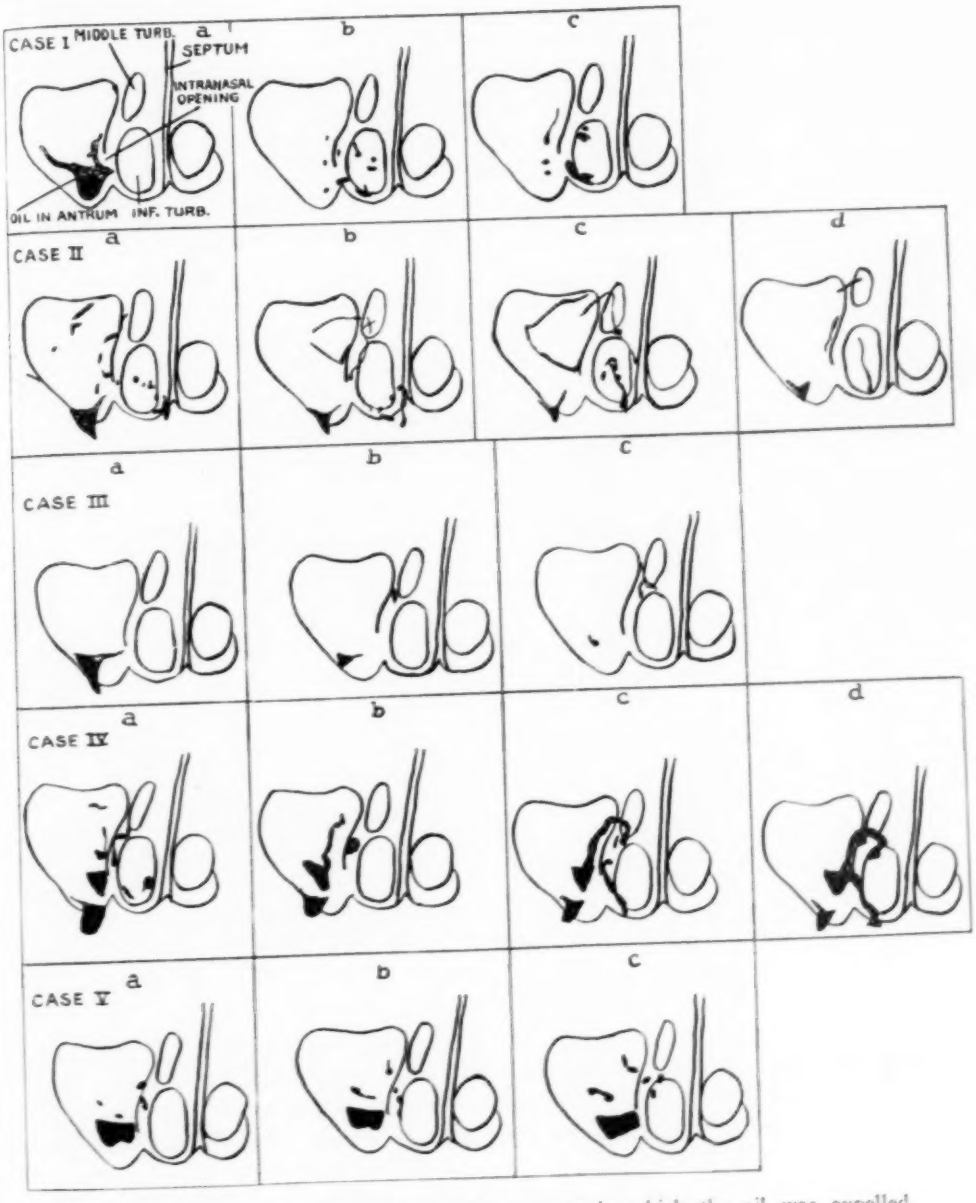

Fig. 1.—The diagrams represent the manner in which the oil was expelled from the antrum. Tracings were made of the original x-ray films showing the various stages. While the intranasal opening does not show on the x-ray film it is represented here by diagram because in the first case the oil outlined it. In case 1, the oil is shown going through both the inferior and the middle meatus openings, but most of the oil traveled through the natural opening. The same is true of case 4. In the other three cases none of the oil was seen going through the intranasal opening.

the opening is present, though reduced in size, and irrigations elicit no secretion. Furthermore, the x-ray view with oil reveals a normal mucosa. The other six do not show a normal mucosa, though three of them are well from a clinical point of view. The others disclose some discharge on irrigation, and the x-rays demonstrate filling defects. In the two who had a radical operation on one side and the intranasal on the other there has been improvement on the side operated on conservatively, but the mucosa is not normal. A study of the side operated on radically was not made.

It is difficult to draw proper conclusions from these cases. A much larger series will be studied and will be more convincing. It can be said, however, that the intranasal operation will succeed more frequently than was thought. It was my opinion, as well as that of a number of other rhinologists, that when patients with chronic sinusitis presented large filling defects the radical operation was the only alternative.

It cannot be said that the polypoid membrane will not respond to the window operation, for I have patients in whom I have viewed polyps with the nasopharyngoscope following the intranasal operation and yet today the mucosa is smooth and clean. This is not a plea to do fewer radical operations. Certainly in 50 per cent of these cases the radical operation should have been performed. One of the patients is a physician who has toxic nerve deafness. He had a chronic antral infection and had the intranasal operation. He thought he was well, because the discharge disappeared and he had no more symptoms from his nose. The hearing remained stationary. A year and a half after the operation the x-rays showed a large filling defect in the lower part of the antrum in spite of the fact that the window was wide open. In this case the entire mucosa should have been removed.

After one has witnessed the experiments of Hilding the question arises as to whether the antral window is of any value where there is a normal opening into the middle meatus. In order to discover whether the window aids drainage, the emptying of the antrum was watched in a series of seven cases. A small amount (generally 2 cc.) of pure iodized oil was injected through the opening in the middle meatus. About ten minutes was allowed to elapse before the first picture was taken, to permit the excess to flow by gravity through the window into the nasal floor. A series of pictures was then made at varying intervals depending on how rapidly the oil moved. The flow was observed until the antrum was empty.

The results of this study show that the cilia wave the oil toward the natural ostium in most cases. Of the seven antrums studied, only one emptied through the window, and this antrum is still diseased in spite of a large window, and the filling defect at the bottom keeps the oil on a level with the window, thus allowing it to flow out by gravity.

In one case the oil did not move in twenty-four hours. In the other five the oil flowed through the natural opening. This bears out clinically the conclusions reached by Hilding experimentally. Of course this is a preliminary report on a small number of cases.

A few patients with chronic disease in whom large filling defects were present have been observed. Each of these patients had a large opening in the middle meatus. Prolonged and persistent treatment produced a cure. I belong to this class. One of my colleagues advised me that a radical operation on the antrum would certainly be necessary, but today the mucosa of my antrum functions normally.

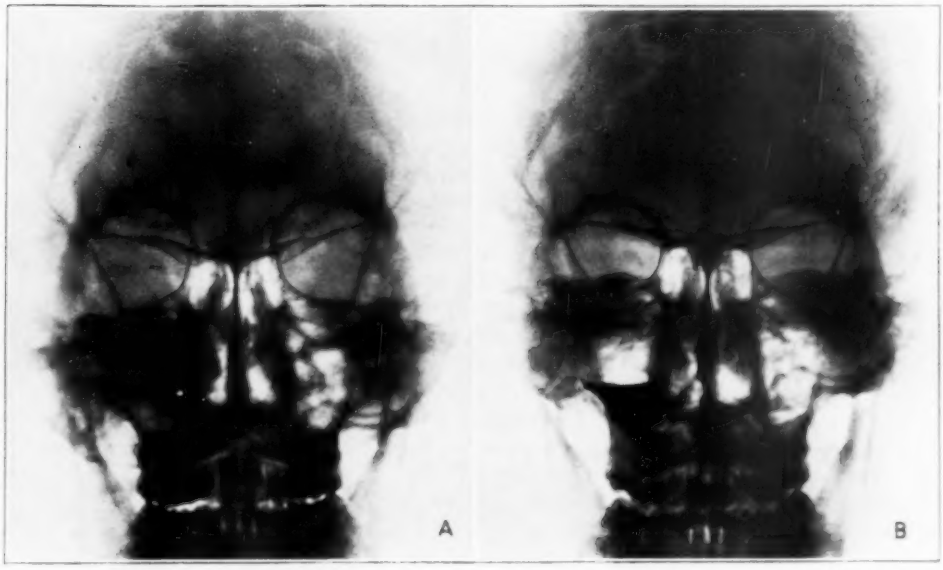

Fig. 2.—*A*, anteroposterior view of the antrum before the intranasal operation; *B*, anteroposterior view of the antrum two months after the intranasal operation.

It is apparent that more careful study of cases before and after operation may point a way to better treatment. The physiology of the mucosa of the sinus is extremely important. Iodized oil delineates the lining of the antrum so that one can visualize it much better than formerly, and to me it is indispensable.

There is a class of cases that respond only to the radical operation on the antrum. These are cases in which the degeneration has gone on for a long time. The polyps may become cystic or hard and resist all treatment. It is possible that the soft polypoid swollen condition of the mucosa may be a defense reaction and that the lining of the sinus may respond to well conducted treatment.

From the cases studied one concludes that the antral window does not aid greatly in drainage.

Carew Tower.

DISCUSSION

Dr. Secord H. Large, Cleveland: It seems to me that when the intranasal operation can be performed with the fine results which Dr. King had, one should try the intranasal operation before doing the radical one.

Dr. King has not taken the ultraconservative position. He says that there are cases in which the radical operation on the antrum is preferable to the intranasal. I agree with him, but I still stick to my old argument that in any radical operation through the canine fossa there is grave danger of interfering with the blood and nerve supply to the pulp of the teeth on that side.

I should like to demonstrate a method that my associates and I have been using for making the window in the lateral wall of the nose. We inject procaine hydrochloride into the inferior turbinate and also the lateral wall of the nose. Then the turbinate is turned upward and we make a quadrilateral flap in the lateral nasal wall. We have one special instrument for making this flap; it is a knife on a curve made by Mueller & Co. With the old Freer submucous knife we are able to join these two lateral incisions. In joining the lateral incisions, on the left side we cut up and on the right side we cut down. This flap is reflected back, and now we are working in an area of bone. After we have reflected and made the opening, we turn this flap in. It has been found that if a submucous flap is turned in, it tends to keep the artificial window open. I think the crux of the operation, and Dr. King did not bring this out, is the packing of the antrum with a 5 per cent iodoform gauze, which is left there from five to seven days. If Hilding is right, we may have to change our procedure by making our opening in the middle meatus.

I think that in a number of these cases the cilia do not perform normally, and that after the intranasal operation has been performed the condition in a number of these chronic cases clears up.

Dr. Louis E. Brown, Akron, Ohio: The cases reported are of insufficient number to serve as a criterion by which to judge whether it is advisable to have all maxillary sinuses examined with the x-rays postoperatively. My limited experience with such a procedure in maxillary sinus involvement, supplemented by many replies to a questionnaire which I sent to both rhinologists and roentgenologists, leads to the conclusion that there is little benefit or definite information to be derived from the postoperative use of the x-rays. Most rhinologists and roentgenologists have no follow-up records or system whereby they can determine what has been accomplished. They have relied almost exclusively on clinical findings to determine whether or not the existing pathologic condition has responded to the surgical procedure, and from the numerous comments on it I feel that the consensus is that roentgen examination of any sinus, particularly the maxillary, as stated, either with or without iodized oil having been injected into it, is of little value postoperatively.

Many men replied that more definite information can be obtained by a diagnostic wash or by a direct observation of the sinus by the use of the nasopharyngoscope, as it is possible in most cases to see just what has been accomplished and what should be done. Either one or all of these, coupled with the clinical findings, was considered of greater importance than the x-ray picture.

After an inflammatory or suppurative process has existed in these sinuses for any length of time, one finds not only a much thickened mucosa, but a definite fibrosis which will give a cloudy picture following operation, even after all clinical symptoms have completely disappeared. It is common knowledge that where these pathologic processes have continued any length of time there results a calcium deposit in the bony wall of the antrum, due to the osteitis, and that this always shows as a dense sinus on the roentgenogram and makes these pictures of little or no diagnostic value postoperatively.

The small number of cases which have been followed by roentgenologic study after operative procedures on the maxillary sinuses does not warrant any definite conclusions on the part of either the rhinologist or the roentgenologist at present. To arrive at a conclusion will require careful records over a long period of time and a greater number of cases studied by the x-rays postoperatively than has been reported.

The only occasion for taking postoperative x-ray pictures of a maxillary sinus would be in cases that have not responded to the operative procedure. This should always make one suspicious of a malignant condition. In such an instance, postoperative x-ray pictures may be of some use and should be resorted to.

Dr. Anderson C. Hilding, Duluth, Minn.: I shall mention only two points briefly. Dr. King asked me to explain the experimental work showing that the drainage of the maxillary sinus occurs through the middle meatus even after a window operation. That was not experimental work. It was some unpublished clinical observations that I happened to speak of once in Cincinnati. Any of you can make this observation. Place a drop of india ink on the floor of the maxillary sinus operated on and watch it for ten or twenty minutes through a nasopharyngoscope entered through the operative window. The result is interesting to see and very instructive. You can see it move toward the ostium. You can also see the increasing rate of speed as it approaches the ostium.

Dr. Large just said that if this is true the cilia drain toward the ostium even after the window is put in and that the window should then be put in the middle meatus. I do not think that that follows. The region right around the ostium in the middle meatus is extremely important, and one does not want to destroy it. It is there that the cilia are most active, and in the animal, at least, vessels and nerves go in through that ostium. It is an important region.

I think it is unnecessary to put it there for another reason. A window is needed for drainage only temporarily, when there is such a large volume of secretion in the antrum that it cannot be handled by the normal physiologic mechanism. In such circumstances it will slide out by gravity through an artificial window into the inferior meatus whence it is carried back into the nasopharynx. When the volume of secretion is reduced, and when the mucous membrane is sufficiently healed to handle the secretion within the sinus once more, it passes out through the natural ostium in the middle meatus even though the artificial window is open. The window then is not of any value but neither is it harmful, and if another infection occurs it again serves the same useful purpose. I think the window in the inferior meatus is a very valuable procedure, but the need for it is a temporary one.

Dr. Harris H. Vail, Cincinnati: I should like to trace for you the progress in the diagnosis and treatment of antrum disease. When I was a house officer in Boston at the Eye and Ear Infirmary, the procedure was to curet the lining of the antrum with a sharp curet until you got white, glistening bone. That was not a good procedure. As improvements were made, it was realized that one should

be careful in stripping the lining of the mucosa. The next process was the use of the opaque oils in diagnosis and the popularity of the window operation.

Hasty, of Nashville, Tenn., has shown that it is not necessary to operate on some antrums, that repeated administrations of iodized oil in an antrum will often clear up a polypoid filling defect.

Dr. King has done a work which I consider revolutionary. I think he will bring out in his discussion that the purpose of the window is to facilitate the frequent treatment of the maxillary sinus.

Another process was the washing out of the antrum through the middle meatus, giving up the rough method of going through the inferior meatus with a large, sharp needle.

One must admit that there has been definite progress in the last fourteen years, and it is due to men like Dr. King and others who are doing experimental work in a practical clinical fashion.

SEQUELAE OF SCARLET FEVER

INVOLVING TEMPORAL BONES, PARANASAL SINUSES, MENINGES, AND LATERAL AND CAVERNOUS SINUSES, WITH NEW BONE FORMATION IN JUGULAR BULB

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The case reported here is recorded because it presented symptoms of every intracranial involvement known to complicate infection of the ear, nose and throat. The pathologic study of the temporal bones and of a block from the sphenoid bone revealed: thrombosis of the lateral and cavernous sinuses; abscess of the carotid artery; labyrinthitis; petrositis, with extension to the meninges, and organization, with new bone formation blocking the jugular bulb.

REPORT OF A CASE

H. C., aged 6 years, entered the St. Louis Children's Hospital five days after the onset of an acute infection of the ears, nose and throat complicating scarlet fever. He had had earache, severe sore throat and vomiting, with high fever at the onset. The past history was irrelevant, except for mumps at 4 years of age and frequent colds in the head. Physical examination revealed a stuporous, poorly nourished child with marked acidosis and anhydremia. The respirations were deep and pauseless; the pulse, rapid, and the temperature 39 C. (102.2 F.). The carbon dioxide-combining power was 18 volumes per cent. The white cell count was 45,000, with a differential count of 10 stab cells, 78 segmented cells and 4 lymphocytes. The chest was clear. The urine showed albumin (2+) with granular and cellular casts. The Addis count showed red and white blood cells and granular and hyaline casts. There was a generalized acute infection of the nasal membrane, nasopharynx and tonsils, with profuse nasal and postnasal discharge. The left ear was full of pus. The membrana tympani was red and full, with a central perforation. The right membrana tympani was thick, red and full. Myringotomy showed pus under pressure. A blood culture was negative. Cultures from the nose and throat showed streptococci. A culture from the right ear showed a few hemolytic streptococci and many hemolytic Staphylococcus aureus organisms; that from the left ear, many hemolytic Staph. aureus organisms.

Acidosis was controlled by the intravenous and subcutaneous injections of molecular sodium lactate. The patient was given frequent intravenous and subcutaneous injections of dextrose and lactate Ringer's solution devised by Dr. Hartmann. The

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The clinical observations in this paper are presented by Dr. Cone from the Oscar Johnson Institute of Washington University, and the postmortem microscopic study, made possible by the Ball Research Fund, was done by Dr. Wolff.

stupor disappeared, and the urine cleared up after forty-eight hours. The fever remained high, between 38 and 40 C. (100.4 and 104 F.). The ears discharged profusely, and there was definite tenderness over the mastoid on each side. Ephedrine and drops of mild silver protein and suction with a rubber catheter were used for the purulent nasal condition. Spinal puncture showed the fluid to be clear and under normal pressure. The cell count showed 13 lymphocytes; the reaction to the Pandy test was negative. Five days after admission (ten days after the onset) edema of the left orbit and of both lids developed, which almost closed the eye. Motion of the globe was normal. The eyegrounds showed edema, with a questionable choking of the left disk. Culture from the eye showed hemolytic Staph. aureus and hemolytic streptococci. A diagnosis of cavernous sinus thrombosis was considered at this time. The next day the edema of the lid and eyegrounds began to clear. The tenderness over the mastoid diminished. The third blood culture, taken six days after admission, was positive for Staph. aureus and streptococci. Eleven days after admission deafness was noted on each side. There was no nystagmus, and caloric tests with water at 68 C. showed a normal response from the right ear and no response from the left, after five minutes. Suppurative labyrinthitis was considered. The attack of mumps two years before was a possible explanation of the dead labyrinth. The discharge from the ears remained profuse. The nose and throat were a little better. The temperature varied from 38 to 40 C. The next day spinal puncture (the second) showed normal pressure with a cell count of 15 lymphocytes and a trace of globulin. Compression of the internal jugular veins gave an equal rise in spinal fluid pressure. It was considered advisable to perform bilateral mastoidectomy and uncover each lateral sinus. Both drum membranes had been destroyed by the massive infection. Thirteen days after admission (eighteen days after the onset) the mastoids were operated on, a hand perforator and burr being used to avoid shock to the labyrinths. The lateral sinuses and dura of the middle fossa appeared to be normal. The mastoids were of the small cell type with diffuse involvement. There was definite necrosis above the horizontal canal and behind the superior canal on the left side. Postoperatively, the general course remained about the same. Eighteen days after admission (five days postoperatively) abscesses of the ankle and scalp developed. These were drained. Beginning November 1 the temperature dropped for the next nine days to 37 and 38 C. (rectal). The deafness persisted. The white cell count dropped to a low of 9,300. The differential count was as follows: Juvenile cells, 5; stab cells, 10; segmented cells, 37; lymphocytes, 45, and monocytes, 1. Thirty days after admission (nineteen days after the onset of the deafness) hearing on the right side returned. The nose and throat were better. The next day the temperature rose to above 40 C. A blood culture showed no growth. The white cell count was 59,100, with a shift to the left. Spinal puncture was performed (November 14). The Queckenstedt test showed a block on the left side with no rise in pressure on compression of the left jugular vein. The left jugular vein was ligated, the lateral sinus opened and a clot removed. There was free bleeding from the posterior limb of the lateral sinus and from the superior petrosal vein. The inferior petrosal vein did not bleed. The temperature remained high. On November 27, forty-five days after the onset, the patient complained of pain in the left side of the face. This was transient, lasting one day.

On December 5, the right disk was blurred and showed a slight elevation. The blood culture showed a pure culture of streptococci. The caloric tests were repeated. There was no response in the left ear, and the right still responded

to ice water, but with definite delay (three minutes). On December 5, the eyegrounds showed a marginal fuzzing of the disk on the right and a little hazing on the left.

On December 8, spinal puncture revealed the spinal fluid to be clear, with 5 lymphocytes and no organisms.

On December 9, the fluid contained 2,000 cells, with 90 per cent polymorphonuclears and no growth on culture. There was a slow rise in the spinal fluid pressure on compression of the right jugular vein. The right internal jugular vein was ligated, and an attempt was made to incise the thickened right sigmoid sinus. There was much bleeding, so the true condition of the sinus could not be recognized. From this time on the child's condition became progressively worse. Organisms (streptococci) were demonstrable in the spinal fluid in direct smears. The eyegrounds showed 1 diopter swelling of the nerve head on the right and only a little on the left.

On December 10, the blood culture was negative.

On December 11, labyrinthotomy on the left side and exploration of the brain were done as a last resort. No purulent drainage could be seen on opening the labyrinth via the basal turn of the cochlea. No abscess was discovered on needling the brain.

The child died six days after the exploration. During this period he presented the typical signs of meningitis. The spinal fluid showed streptococci on direct smears, and the cell count rose to 25,000.

During hospitalization, ten small blood transfusions of from 110 to 300 cc. were given. Dextrose and lactate Ringer's solution devised by Dr. Hartmann were used frequently to control dehydration and shock. Twenty cubic centimeters of scarlet fever antitoxin was used during the first four days of hospitalization. Only three of the ten blood cultures were positive.

Postmortem Microscopic Observations.—The following material was obtained at autopsy for microscopic observation: the petrous portions of the right and left temporal bones, a sizable block from the sphenoid, a small fragment of the ethmoid and a piece of brain stem at the level of the exit of the eighth nerve. These tissues were embedded in pyroxylin (celloidin) and sectioned at 20 microns.

Left Temporal Bone: Middle Ear. The mastoid cavity was free from pus in the center, but necrotic tissue was seen around the periphery. Free pus occurred in the para-antral cells. These cells were lined with edematous mucosa, the vessels of which showed marked congestion. Sections 131 to 175 showed that the dura surrounding the vessels of the subarcuate fossa was in direct communication with the infected submucosa of the mastoid. Thrombi occurred in these vessels. No infiltration of the dura was observed. A thrombus was observed in the superior petrosal vein. Sections 407 to 531 showed a fistula into the dura through the medial wall of the mastoid. The fistula terminated primarily in the intradural space, which looked much like the saccus endolymphaticus but which could not be definitely connected with the ductus endolymphaticus.

Sections 221 to 263 (figs. 1 and 2) showed a pathologic dehiscence under the gasserian ganglion through which pus from the infected marrow of the petrous apex was passing to the epidural and intradural regions. The epidural abscess could be traced posteriorly to the region of the geniculate ganglion.

The middle ear cavity was filled with granulation tissue. The tensor tympani muscle had undergone fatty degeneration. A slight vestige of the stapedius muscle remained near its origin (sect. 531). The foot plate of the stapes was

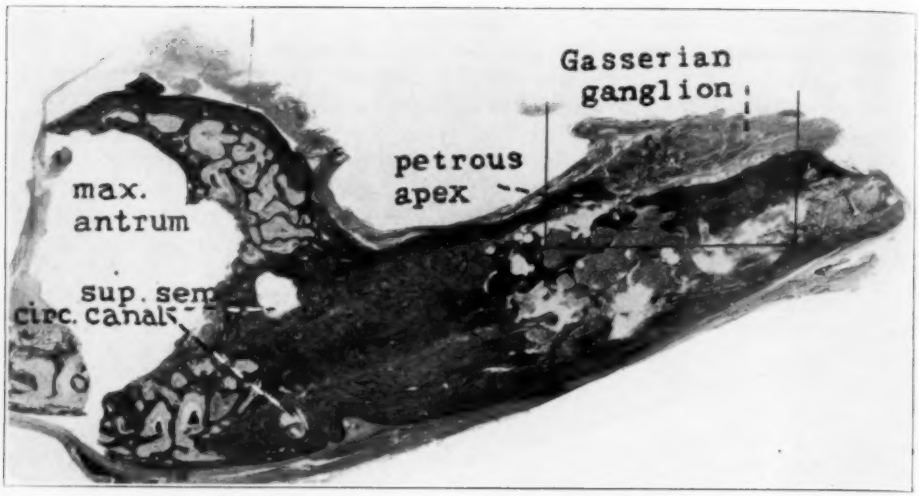

Fig. 1 (sect. 263).—Pathologic dehiscence under the gasserian ganglion.

Fig. 2 (sect. 263).—Detail of the region of the gasserian ganglion.

fractured and dislodged from the oval window, pus and granulation tissue with fragments of bone entering the vestibule at this level (fig. 3, sect. 417). The bony facial canal exhibited a sizable aperture posterior to the oval window. The tissue around the facial nerve was edematous, and the accompanying vessels were congested. The sinus tympani was filled with granulation tissue. The niche of the round window was also filled with pus and granulation tissue. Figure 4

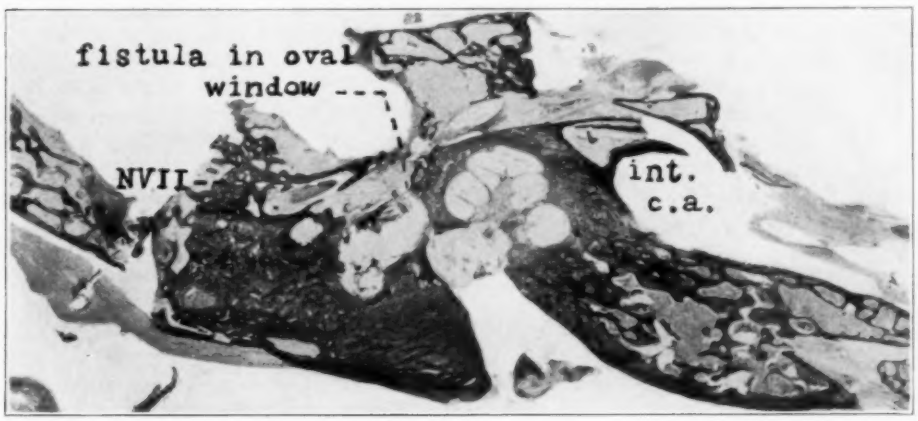

Fig. 3 (sect. 417).—Pus is shown invading the midmodiolar cochlea, but not markedly.

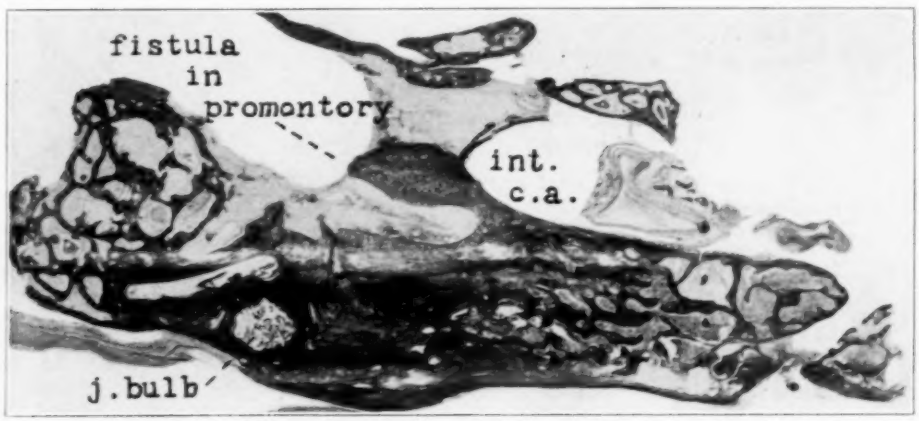

Fig. 4 (sect. 541).—Niche of the round window and basal coil filled with pus and granulation tissue.

(section 541) shows a fistula extending through the promontory. No remnant of the membrane of the round window could be discerned.

The hypotympanum contained a mass of free pus, and at this level the jugular vein was filled with a massive infected thrombus. The wall of the vein had degenerated, and the pus was in direct contact with the nerves from the petrosal ganglion. The bony wall of the jugular bulb at a higher level was invaded by

trabeculae of new-formed bone (fig. 5, sect. 614). This was estimated to be a process of about three weeks, according to Dr. McCordock.

Inner Ear. At its superior level the medial limb of the superior semicircular canal showed the perilymphatic tissue packed with red blood cells, while the endolymphatic canal was relatively clear, although its wall was degenerating and the fluid contained stained pink indicating a serous labyrinthitis. The lateral limb of the canal contained pus in both systems, as did the median at a lower level. A fistula had been made by operative procedure in the horizontal canal just posterior to the ampulla. Minute vessels in the canal and the lower level of the ampulla evidenced beginning organization tissue. Sections 366 to 385 showed the interesting phenomenon of relatively well organized tissue in the perilymphatic space of the horizontal canal, while the endolymphatic space was filled with pus. The wall separating these two spaces was intact.

The posterior semicircular canal contained free pus in both the perilymphatic and the endolymphatic spaces. Here also the wall between the two canals was

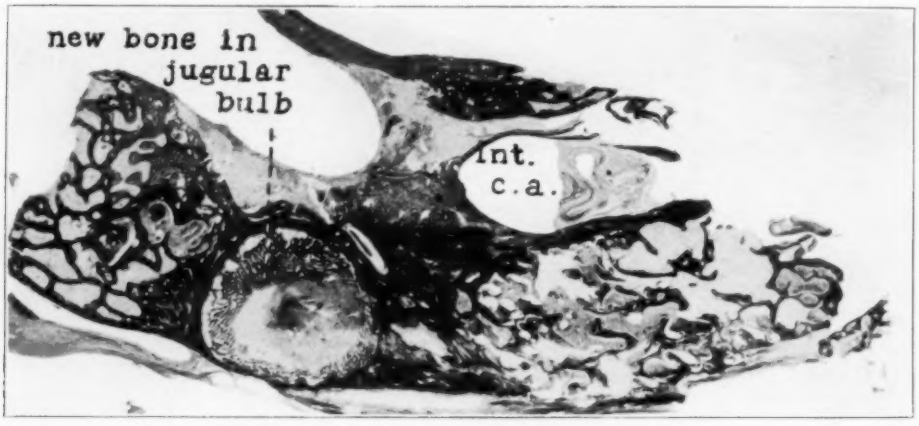

Fig. 5 (sect. 614).—Infected thrombus in the jugular bulb and new trabeculae of bone forming.

preserved. At the level of the oval window a fistula had been created by operative procedure. The foot plate was dislodged and fragmented. Necrotic tissue, fragments of bone and pus extended into the vestibule.

In the cochlea there were heavy infiltration of the spiral ganglion cells and congestion of the vessels. Liquefaction necrosis had destroyed the organ of Corti in all turns, but most completely in the middle turn. Reissner's membrane was in some regions glued to the stria and in others to the tectorium. As noted, a fistula had been made in the promontory. This showed organization tissue in part of the course of the basal turn. Some free pus was seen in the upper part of the basal turn and in the middle turn, but on the whole these regions were surprisingly free from a suppurative condition. The endolymphatic duct contained some infiltration, and the lumen appeared more or less blocked with scarred and edematous tissue. The lumen of the aqueduct of the cochlea and the internal auditory meatus were filled with pus. The muscular walls of the vessels, particularly those in the dura, were greatly thickened in the meatus.

Right Ear: Middle Ear. On the right side a large part of the epitympanum was filled with a web of delicate scar tissue. The malleus and incus were embedded in this tissue, and patches of infiltration occurred in it. The ossicular joint was completely demolished. As on the left side the dura of the subarcuate fossa extended to the mastoid cells but was not infiltrated. The vessels were congested in this region. The petromastoid canal (suture) was still present and contained pus. An infected thrombus was seen in the superficial petrosal vein, and pus occurred in the gasserian ganglion. No apical dehiscence was observed on the right.

As on the left side, the tensor tympani was destroyed, only a little of the tendinous attachment remaining. The canal was filled with pus. The lumen of the bony eustachian tube contained pus.

Above the level of the drum membrane (sects. 332 to 342) pus was seen extending into the external canal. The membrana tympani had been destroyed below this level, only the perimeter remaining. Under the epidermis on the posterior border pus extended to the internal canal. The middle ear cavity proper was filled with free pus and webs of scar tissue. Niches of oval and round windows exhibited this condition. The membrane of the round window was completely demolished, and pus was extending into the basal turn of the cochlea. The foot plate was bowed in two places and was greatly thinned.

The hypotympanum contained the same type of tissue as occurs in the epitympanum. It also was infiltrated. Blood and pus were in the facial canal.

Inner Ear. A serous labyrinthitis was evident in the superior canal. At the level of the ampulla infiltration was present under the crista and primarily in the perilymphatic tissue. Breaking down of the perilymphatic trabeculae was evidenced in the horizontal canal (sect. 282).

Cochlear ganglion cells were heavily infiltrated and were undergoing liquefaction necrosis. Vestibular ganglion cells were in a like condition, as the internal auditory meatus was filled with pus.

The vestibule showed an early purulent condition as did also the cochlea. The organ of Corti showed liquefaction, but much of the cochlea could not be studied because of poor technic. The presence of a purulent condition was observed, however. The endolymphatic duct on this side contained a pink-staining fluid in the lumen and infiltration of the epithelium. More peripherally, pus cells were seen in the lumen, and scar tissue was present.

Sphenoid: The block of the sphenoid showed the body of the sphenoid extending from the region just posterior to the cavernous sinus forward to the beginning of the sphenoid sinuses. It included 1,544 sections (at 20 microns). Some of the basal cartilage of the skull was seen in the sections. The body of the sphenoid was filled with the blood-forming type of marrow, with bony trabeculae forming an open network in the marrow. There were evidences of edema or excess liquid state in the marrow. Figures 6 and 7 (sect. 436) showed an abscess in the cavernous sinus on the left. Pus from this abscess infiltrated all the soft tissue in the region extending both anteriorly and posteriorly. At the level of section 316 the internal carotid artery appeared completely collapsed, while at section 677 (fig. 8) the lumen was expanded and showed early organization. In both regions the tissue surrounding the artery was heavily infiltrated.

The mucosal lining of the left sphenoid sinus had been completely removed, but that of the right was still in situ. In certain regions frank pus was seen in the lumen. There was edema of the submucosa. Spontaneous dehiscences or apertures occurred in the sphenoid bone between it and the orbital cavity. There was evidence of edema in the orbital cavity at the orbital end of these apertures.

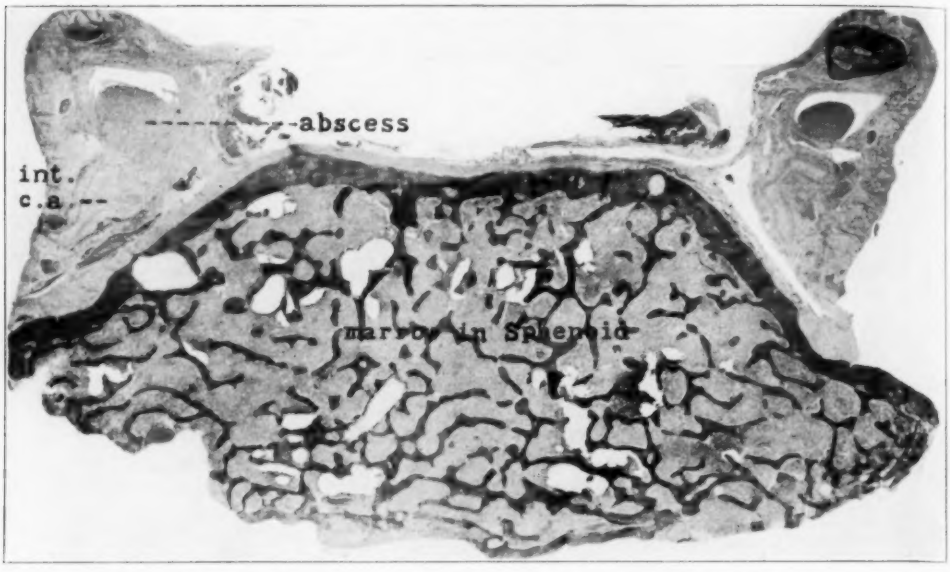

Fig. 6 (sect. 436).—An abscess in the cavernous sinus on the left side.

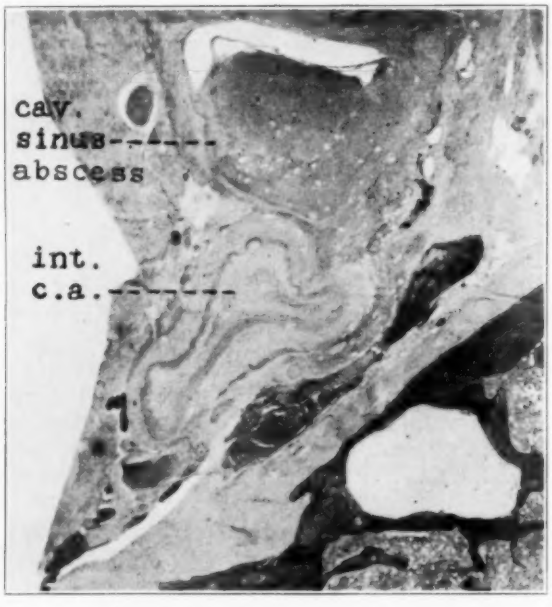

Fig. 7 (sect. 436).—Detail of the abscess in the cavernous sinus.

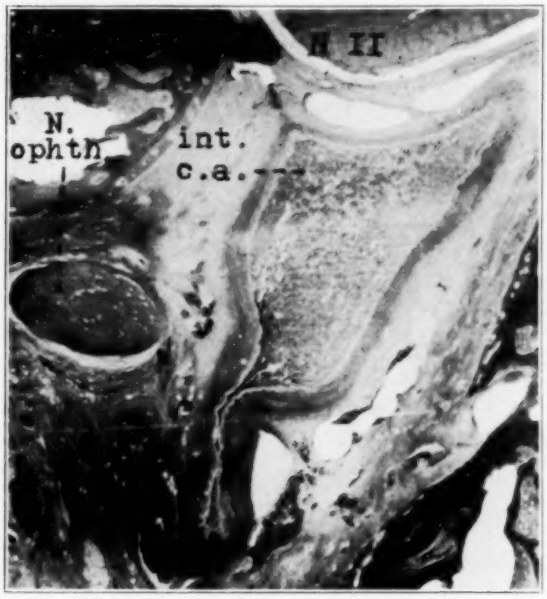

Fig. 8 (sect. 677).—Organization in the internal carotid artery.

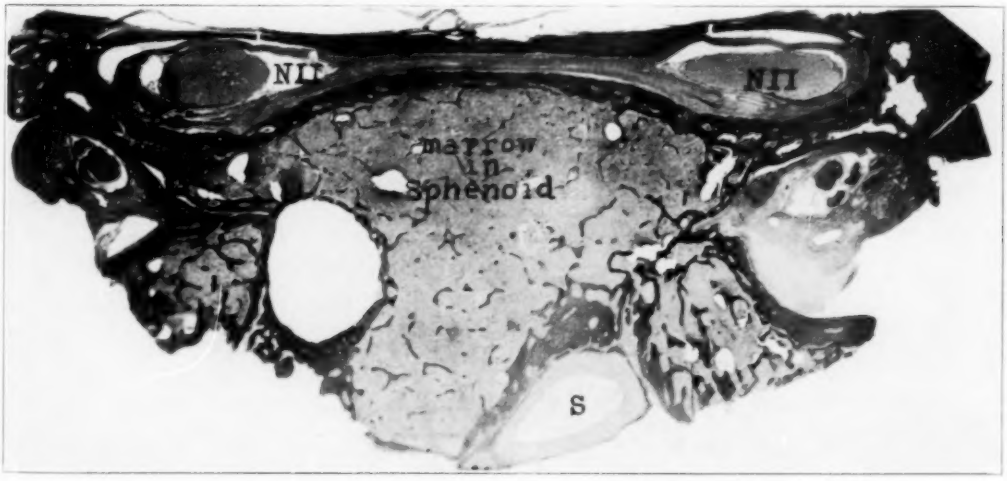

Fig. 9 (sect. 847).—Sphenoid bone anterior to the part shown in figure 7. The left sinus was stripped of its mucosa at autopsy.

Ethmoid: The ethmoid cell obtained showed pus in the lumen and a generalized infiltration of subepithelial tissue, mostly with small round cells. The ciliated epithelium was for the most part intact but was sloughed off in a few places. Delicate trabeculae of bone similar under low power magnification to that of the region in the jugular bulb, except for the fact that no alinement of osteoblasts was evident, occurred in this tissue. These were interpreted as normal ethmoid bone.

Brain Stem: The neurons in the region sectioned were quite normal. The nuclei were centrally placed and stained well. Edema was seen along the nerve fibers. The meninges surrounding the brain stem were heavily laden with pus cells. Among these were observed several exceptionally large mononuclears with eccentric nuclei and globular cytoplasm.

RÉSUMÉ

A review of the entire course does not permit definite interpretation of the sequence of involvement. The early edema of the lids and changes in the eyegrounds suggest that the cavernous sinus may have been the first venous involvement. This thrombosis could have followed the acute sinusitis and disease of the sphenoid bone or have been secondary to the involvement of the petrous pyramid and the mastoid.

Eagleton [1] reported six pathways for involvement:

1. Ophthalmic (anterior)
2. Pterygoid (anterior-inferior)
3. Sphenoid (mesial)
   (*a*) Caries of the sphenoid
   (*b*) Thrombosis of the veins through the sphenoid roof
4. Aural (posterior)
   (*a*) Thrombosis of the inferior petrosal
   (*b*) Caries of the deep cells at the apex of the petrous pyramid
5. Tonsillar (posterior-inferior)
   (*a*) Via pterygomaxillary fossa by way of an ascending thrombophlebitis of the jugular vein
6. Carotid venous plexus with direct infection into the lumen of the cavernous sinus

"All six types may pass from one to another because of the free anastomotic communication of the venous radicles with each other."

Eagleton [2] reported the possibility of direct extension from an apical cell.

Courville and Nielsen [3] stated: "While thrombosis of the cavernous sinus may be secondary to apicitis petrosa, such cases must be some-

1. Eagleton, W. P.: Cavernous Sinus Thrombophlebitis, New York, The Macmillan Company, 1926, p. 6.

2. Eagleton,[1] p. 36.

3. Courville, C. B., and Nielsen, J. M.: Fatal Complications of Otitis Media: With Particular Reference to the Intracranial Lesions in a Series of Ten Thousand Autopsies, Arch. Otolaryng. **19**:467 and 478 (April) 1934.

what rare." They also stated [4] that "of all the intracranial complications of apicitis petrosa, septic meningitis is the most common." Included in their review are the reports of three cases of involvement of the carotid canal and internal carotid artery secondary to infection of the petrous pyramid. They stated [5] that "a pericarotid abscess may result at times associated with involvement of the arterial wall (arteritis) or thrombosis of the pericarotid network of small veins." Two of the reports were of cases of thrombosis of the internal carotid artery.

Kopetzky and Almour,[6] in presenting the differential diagnosis of suppuration of the petrous tip, stated that it must be differentiated from disease of the nasal accessory sinus, lateral sinus thrombosis, cavernous sinus thrombosis, thrombosis of the superior petrosal sinus, acute labyrinthitis and a reinfection of the mastoid process. In an "acute necrotic" involvement of the ear, nose and throat, as occurred in our case, and as Kopetzky and Almour [7] stated is seen in scarlet fever, the differential diagnosis is impossible.

Suppuration of the petrous pyramid is covered in detail by Kopetzky and Almour.[8] One of the points of special interest relating to our case is ocular pain.[9] The transient labyrinthine symptoms in their case [10] and the absence of paralysis of the sixth nerve are additional points of interest to us. Of the latter point, they stated, "its presence in such cases is the exception rather than the rule." [11]

Eagleton [12] referred to pain behind the eye as being significant of irritation of the dura over the petrous apex. He also noted the association of infection of the labyrinth in suppuration of the petrous apex. He stated: [13] "In two of my cases the labyrinthine involvement was probably secondary to the infection of the apex and not the cause of it."

CONCLUSIONS

1. Following the presence of an infected thrombus, new trabeculae of bone may be formed in and may occlude the jugular bulb. So far

4. Courville and Nielsen,[3] p. 466.

5. Courville and Nielsen,[3] p. 463.

6. Kopetzky, S. J., and Almour, R.: Suppuration of the Petrous Pyramid, Ann. Otol., Rhin. & Laryng. **40**:175 (March) 1931.

7. Kopetzky and Almour,[5] p. 161.

8. Kopetzky and Almour,[5] p. 157.

9. Kopetzky and Almour,[5] p. 158.

10. Kopetzky and Almour,[5] p. 164.

11. Kopetzky and Almour,[5] p. 170.

12. Eagleton, W. P.: Unlocking of the Petrous Pyramid for Localized Bulbar (Pontile) Meningitis Secondary to Suppuration of the Petrous Apex, Arch. Otolaryng. **13**:403 (March) 1931.

13. Eagleton,[12] p. 402.

as we know, this observation has not previously been recorded in the literature.

2. Subjective symptoms in children with apicitis may be transient.

3. In an acute necrotic infection following scarlet fever the intracranial vascular involvement may be extensive.

4. Thrombosis of the cavernous sinus, in this case, may have been secondary to apicitis, sinusitis or inferior or superior petrosal thrombophlebitis, or by way of the pericarotid venous network.

TRANSPHENOIDAL INJECTION OF IODIZED POPPY-SEED OIL INTO A HYPOPHYSEAL CYST

REPORT OF A CASE

FRED H. LINTHICUM, M.D.
LOS ANGELES

The transphenoidal injection of iodized poppy-seed oil 40 per cent into hypophyseal cysts is not a routine procedure. The results obtained were as surprising and unlooked for as they were unique and bizarre in my experience. They did, however, lead to some observations and results of interest.

REPORT OF CASE

A man, 42 years old, came to the Good Hope Clinic complaining of failing vision, which had its onset in August 1931, three months before he was first seen. His previous history was not relevant, except for the fact that for the past two years he had been suffering from what he described as "drawing pains" in the back of his neck. These pains were particularly noticeable when the patient attempted to read without glasses or when he contracted a cold. They occasionally radiated to the temporal regions and the root of the nose and suggested in distribution irritation of the sphenopalatine ganglion.

Attention was first called to the patient's blurred vision when he broke his glasses two months before his visit to the clinic. During this period he was unable to read, because the print was blurred and the letters "ran together." This condition became rapidly worse. He first came under the observation of Dr. Ray Irvine. His vision was so poor at this time that it was difficult to get accurate perimetric measurements. His color fields could not be taken. Using a 3 mm. target, there was found to be concentric constriction of the right field of between 20 and 30 degrees. There was left hemianopia in the left eye. His vision at this time was 20/70 in the left eye and 20/200 in the right eye. (There had been an injury to the left eye in childhood.)

On account of the ocular findings a roentgen examination was made. The sella turcica was faintly outlined. The anterior clinoid process was irregular, and the posterior clinoid process, together with the dorsum of the sella, suggested erosion (fig. 1). There was also a pushing down of the floor of the sella, with apparent erosion into the sphenoid sinus. The left antrum was clouded, and the Granger line was absent.

General physical examination resulted in no finding of moment. There was a systolic murmur at the apex and base of the heart. The blood pressure was 160 systolic and 106 diastolic. The Wassermann reaction was negative. The blood picture and the urine were normal.

Because of roentgen evidence of sinus disease, the patient was directed to the department for conditions of the ear, nose and throat. He gave a history of nasal

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Read in part before the Western Section of the American Laryngological, Rhinological and Otological Society, Inc., Portland, Ore., Jan. 13, 1934.

occlusion, which was more marked on the right side, and postnasal mucoid discharge. There had been a tonsillectomy and turbinectomy. Headaches had been present for two years. He described these as pain and stiffness in the back of the neck radiating into the occiput and occasionally into the temples or the root of the nose.

Examination of the anterior nasal chambers showed evidence of chronic sinus disease. Examination with the nasopharyngoscope demonstrated a bulging in the right pharyngeal vault practically obliterating the fossa of Rosemüller. There was no evidence of ulceration.

The antrums were next irrigated. The fluid was returned clear from the right side, but that from the left side contained several drachms of milky pus. Attention was then directed toward the posterior sinuses. On account of the abnormal appearance in the region of the right sphenoid sinus, about 5 cc. of iodized oil was injected without pressure into this cavity by Dr. O. H. Homme. When none of the oil appeared in the throat, about 4 cc. more was put in, still with no evidence

Fig. 1.—Roentgenogram showing erosion of the clinoid processes and floor of the sella.

that the cavity was filled. Thinking that we were dealing with an excessively large cell or a dehiscence into the opposite sinus we introduced several more cubic centimeters. Finally our discretion surmounted our curiosity, and the patient was taken to the roentgen department to determine where the unusual amount of injected oil had gone. Our surprise can be imagined when the accompanying roentgenograms were developed (fig. 2).

A large bilobulated cavity above the sella had been filled with the oil. The shadow on the right was approximately in the midline, circular and on a higher level than the left lobe, which was much more irregular in shape; it extended laterally on a much lower level to a line corresponding to the outer rim of the orbit and posteriorly to the level of the external auditory canal. A channel filled with the oil may be seen extending from the sphenoid cavity to the lobes of the cyst.

The next step contemplated was exploration of the sphenoid cavity, but before doing this a small piece of tissue was removed from the interior of the sinus for

biopsy. Dr. Roy Hammack reported the section to show the presence of a typical adenoma of the pituitary gland; this was chromophobe, with a suspicion of malignancy (fig. 3).

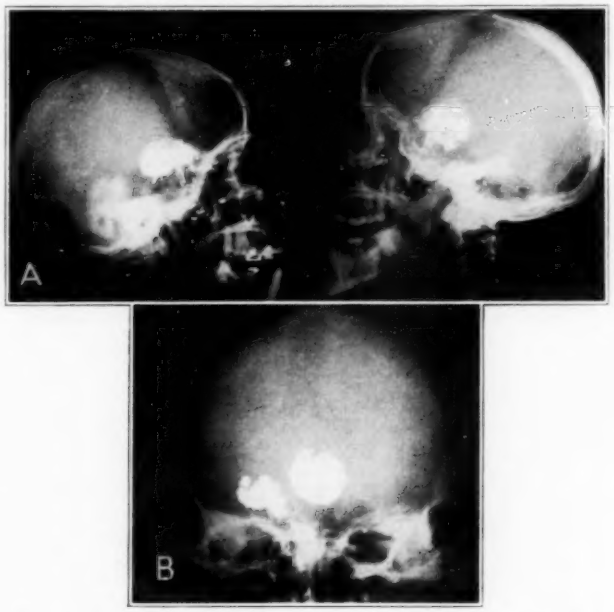

Fig. 2.—Roentgenograms showing a large cystic excavation on the right and a smaller and lower one on the left, both filled with iodized oil.

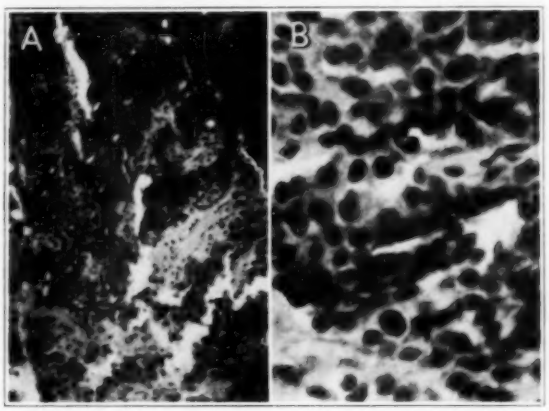

Fig. 3.—Photomicrographs of typical chromophobe adenoma: *A*, high power magnification; *B*, lower power magnification. Tissue for biopsy was obtained through the sphenoid sinus.

Another series of roentgenograms were made about three weeks later. There was no decrease in the amount of iodized oil as compared with the first pictures.

The patient apparently suffered no inconvenience from its presence. Presumably, the oil had become trapped in the cavities and was prevented from draining out by some type of ball-valve action at its point of entrance.

Owing to the fact that at this time we elicited from the patient the fact that there had recently been some equilibratory disturbance, he was referred to the vestibular or neuro-otologic department for study. As may be seen from figure 2 *A*, the shadow of the iodized oil on the left side extended posteriorly for a distance sufficient to cause pressure on adjacent structures conveying vestibular pathways.

An audiogram showed hearing within normal limits (fig. 4). The vestibular findings (table 1) in summary were: spontaneous horizontal nystagmus to either side; spontaneous rotatory nystagmus to the left on looking down; postrotatory nystagmus, which was faint, especially after turning to the left; postcaloric nystagmus, which was poor from the right ear and subnormal but somewhat stronger from the left ear; absence of constitutional symptoms on both sides, and abnor-

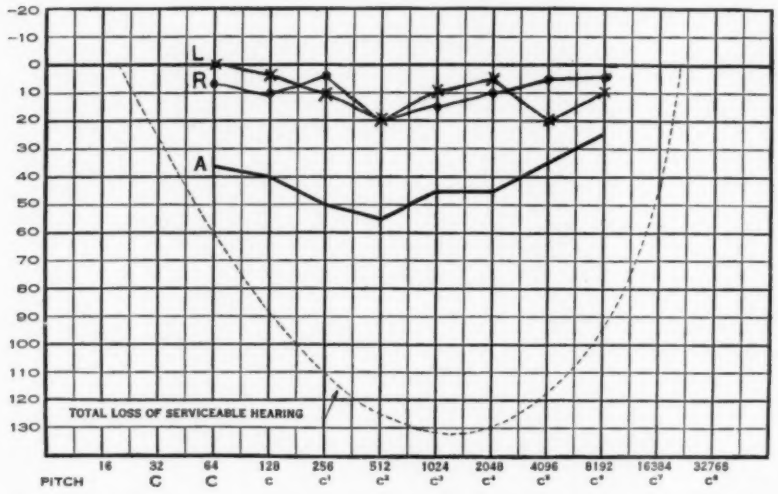

Fig. 4.—Audiogram taken on Jan. 15, 1932, showing hearing within normal limits. The arrow indicates normal hearing. *L* is the curve for hearing on the left, and *R* for hearing on the right. *A* is the reading for a person of normal hearing when tested with the D-80904 bone conduction receiver.

malities in past-pointing (crossing or absence). Sense of motion was practically absent.

Six months later, after the operation, the vestibular picture had changed to a degree (table 2). The spontaneous nystagmus had disappeared. There were spontaneous past-pointing to the left with the left arm and marked disproportion between the duration of the after-turning nystagmus and the after-turning of motion-sensing. The postcaloric nystagmus from the right vertical canals was of mixed vertical and horizontal type. There were practically no responses of any kind after douching the left ear, whereas before the nystagmus from both sets of canals had been somewhat small but definite. It may be recalled that on this side the lobe of the tumor was on a much lower level and extended much farther posteriorly than the one of the opposite side. It is possible that the pressure on adjacent vestibular pathways on the left side might account for the abolition of function of the left labyrinth.

TABLE 1.—*Results of Vestibular Test on Nov. 24, 1931, Previous to Operation*

Spontaneous Reactions		Pointing	
Nystagmus		Right Arm	Left Arm
On looking ahead On looking to right ← small On looking to left → small On looking up On looking down	Station Head to right Head to left	Touch	Touch
	Turning		
To right, small and irregular Duration, 20 seconds	Nystagmus Past-pointing Sensing of motion Nausea Sweat Pallor		
To left, very poor Amplitude practically imperceptible	Nystagmus Past-pointing Sensing of motion Nausea Sweat Pallor		
	Douching		
Right ear with head up ↷ Amplitude very small After 30 seconds; 1 minute Total douching, 3 minutes	Nystagmus Past-pointing Sensing of motion subnormal Falling 0 Nausea 0 Sweat 0 Pallor 0	4 inches to right	Touch
Head back → Amplitude from good to fair		6 inches to right	Touch
Left ear with head up ↶ ← Amplitude irregular and small, but definite After 55 seconds Total douching, 2 minutes	Nystagmus Past-pointing Sensing of motion slight Falling 0 Nausea 0 Sweat 0 Pallor 0	Touch	8 inches to left
Head back ← Amplitude irregular, fair and definite		5 inches to right	8 inches to left

TABLE 2.—*Results of Vestibular Test on May 24, 1932, After Operation*

Spontaneous Reactions		Pointing	
Nystagmus		Right Arm	Left Arm
On looking ahead 0 On looking to right 0 On looking to left 0 On looking up 0 On looking down 0	Station Swaying Head to right to Head to left left	Touch	3 inches to left
	Turning		
To right → very slow Amplitude fair Duration, 16 seconds	Nystagmus subnormal Past-pointing Sensing of motion, 23 seconds Nausea 0 Sweat 0 Pallor 0		
To left ← slow Amplitude very small Duration, 11 seconds	Nystagmus subnormal Past-pointing Sensing of motion, 21½ seconds Nausea 0 Sweat 0 Pallor 0		
	Douching		
Right ear with head up ↷	Nystagmus perverted Past-pointing	4 inches to right	Touch
After 30 seconds Total douching, 2 minutes	Sensing of motion subnormal Falling 0 Nausea 0 Sweat 0 Pallor 0		
With head back → small Amplitude poor		8 inches to right	3 inches to right
Left ear with head up, none Total douching, 3 minutes	Nystagmus absent Past-pointing 0 Sensing of motion 0 Falling 0 Nausea 0 Sweat 0 Pallor 0	3 inches to left	3 inches to left
With head back, a few jerks Amplitude practically 0		Same as spontaneous	Same as spontaneous

Dr. Lewis Fisher,[1] in analyzing the vestibular reactions in eleven cases of suprasellar lesions (and on account of its size one must consider this tumor a suprasellar growth anatomically, if not etiologically), stressed especially the disproportion between the duration of after-turning nystagmus and sensing of motion and the interference with the postcaloric responses from the vertical canals, usually on one side only. In this instance both these phenomena are to be noted.

The next step was to obtain a neurologic report. This was made by Dr. Douglas Eaton and was as follows: "The head shows a high-pitched note throughout, which is somewhat greater in the left parietal region. There is a slight, fine tremor of the extended fingers. Sense of smell is absent on the right side. Taste is normal. The pupils are slightly irregular. The disks show optic atrophy, which is somewhat greater on the right. There is no choking. The right palpebral fissure is smaller than the left, with some ptosis of the right upper eyelid. Speech is thick. Muscle tone is generally poor. There are abnormal reflexes. Gait, posture and balance are normal. The impression is that of tumor of the pituitary gland."

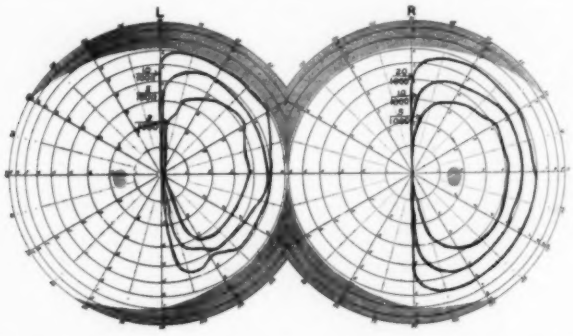

Fig. 5.—Uncorrected visual fields before operation, on January 29; vision in the left eye was 20/70, and the patient was able to see a moving hand at 18 feet (5.5 meters) with the right eye.

Approximately fourteen weeks after the patient was first seen in the Good Hope Clinic he was admitted to the Los Angeles General Hospital, where he underwent a thorough examination by Dr. Cyril B. Courville. Particular emphasis was laid on evidence of glandular dysfunction. The additional fact was brought out that bright lights were particularly troublesome. There was a fine nystagmus on looking up and to the right. The only evidences of polyglandular disturbance were a skin somewhat finer than normal for a man of 42 years and a characteristically fine wrinkling of the skin of the face. There had been a marked increase in appetite during the previous month, with a gain in weight of 6 pounds (2.7 Kg.). There was no evidence of associated suprarenal disease. For eight months previously an increasing tendency to drowsiness was noted; the patient fell asleep when he sat down to read. His visual fields at this time displayed typical homonymous hemianopia (fig. 5). Sugar tolerance was as follows: during fasting,

1. Fisher, Lewis, and Glaser, M. A.: New Vestibular Complexes for Localization of Lesions of the Brain: An Analysis of One Hundred and Thirty-Nine Verified Lesions, Arch. Neurol. & Psychiat. **21**:876 (April) 1929.

102 mg. of sugar; one hour after eating, 192 mg.; two hours after eating, 122 mg.; three hours after eating, 104 mg. The basal metabolic rate was —4. A diagnosis of a chromophobe adenoma of the pituitary gland was made, and the patient was operated on by Dr. Carl W. Rand.

Through a right frontal approach the chiasmal region was exposed. The right optic nerve was white, under tension and surrounded by grayish tissue, supposedly pituitary tumor. The suprasellar region was not explored, owing to the poor condition of the patient. Two weeks later a second stage operation was performed through the same route. A reddish irregular mass of tumor tissue was found about the chiasm and extending over into the region of the right temporal lobe. The tumor apparently extended posteriorly above the chiasm. The right optic

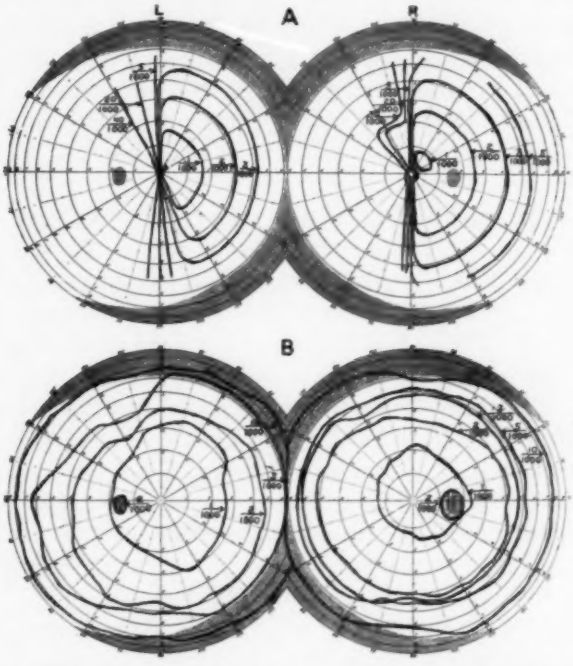

Fig. 6.—*A*, corrected visual fields after operation, on March 2; vision in the left eye was 20/30 and in the right eye 5/200. A Bjerrum screen was used, and the patient cooperated well. *B*, uncorrected visual fields on August 3; vision in the left eye was 20/30, and with the right eye the patient was able to see a dark outline of the letter L, but was unable to name the letter.

nerve lay over the right internal carotid artery as it entered the skull from the circle of Willis. Pressure from below had flattened this optic nerve so that it appeared to be a mere ribbon of yellowish-white tissue as it entered the right foramen. This was undoubtedly due to upward pressure of the tumor mass transmitted through the artery to the nerve. A puncture of the lamina terminalis failed to reveal any considerable amount of fluid. The exposed part of the tumor was removed. The greater mass of the tumor lay so far posteriorly that it was deemed inadvisable to attempt to remove it. Recovery was uneventful.

The patient was able to return to work within a few months coincidentally with improvement in his vision, as shown by the accompanying charts (fig. 6).

COMMENT

Tumors of the hypophysis are not rare. Of the two types of intrasellar adenomas, eosinophilic and chromophobic, the latter forms the larger group. More rare, however, is cystic degeneration of these tumors. The incidence of this condition is from 15 to 20 per cent, while homonymous hemianopia such as has been described in this case is met with in only about 2 per cent of adenomas. I have been unable to determine the incidence of erosion through the roof of the sphenoid sinus.

In this case we had the unusual experience of investigating a tumor of the brain, a growth involving the pituitary gland, the size, shape and extent of which we were able to determine before operation by means of radiopaque oil injected through a defect in the roof of the sphenoid sinus. It was furthermore possible through the same route to obtain material for biopsy and demonstrate microscopically before operation that we were dealing with a chromophobe tumor of the hypophysis.

Periodic roentgen examinations during the next year and a half demonstrated the fact that considerable iodized oil still remained in the part of the cyst which was not removed, with apparently no ill effects. In a recent interview the patient stated that his headaches had disappeared; his vision was better than it had been since long before his operation, and he had been able to work constantly. Roentgenograms at present show the iodized oil diminished in amount but still present.

At the time this communication was read before the Western Section of the American Laryngological, Rhinological and Otological Society it seemed improbable that such a chain of events could lead to a duplication of the result and findings reported. Since then, however, Dr. William Turnley [2] has published a report of a case which is similar in many respects.

Since erosion of the floor of the sella is not uncommon, one is led to conjecture whether this may not be a means by which the size, position and shape of cystic tumors of the hypophysis may occasionally be determined by the injection of iodized oil through dehiscences in the roof of the sphenoid sinus.

523 West Sixth Street.

2. Turnley, W. H.: Spontaneous Decompression of a Tumor of the Pituitary Area of the Brain, Laryngoscope **40**:299, 1934.

Abstracts from Current Literature

Ear

DEAFNESS IN NASSAU COUNTY SCHOOL CHILDREN. GERARD H. COX, M. J. & Rec. **138**:452 (Dec. 20) 1933.

Seven hundred and forty-nine pupils were examined. Thirty-eight, or 5.07 per cent, were found to have defective hearing. Twenty-three, or 3.007 per cent, had unilateral deafness, and fifteen, or 2 per cent, had bilateral deafness. Fowler's procedure for making the tests on the children is given verbatim in the article. Tubal catarrh and chronic catarrhal otitis media, associated with hypertrophied tonsils and adenoids, accounted for the largest group of those hard of hearing.

The author's statistics show the importance of employing this test routinely in the public schools at least once a year, in order that pupils with mild grades of defective hearing may be identified and treated while the disease is in the incipient stage.

WILLIAMSON, New Orleans. [AM. J. DIS. CHILD.]

VERTIGO. W. R. BRAIN, J. Laryng. & Otol. **49**:153 (March) 1934.

Aural vertigo and its differentiation from vertigo due to lesions elsewhere are the concern of Brain in this paper. There is probably no feature absolutely pathognomonic, but a sense of rotation of the patient or his surrounding with diminished excitability of the semicircular canals, deafness and tinnitus are present as a rule. The rotated posture of the head is a useful sign of a lesion of the labyrinth and has been produced in experimental animals. The principal conditions from which aural vertigo must be differentiated are lesions of the eighth nerve and of the pons and medulla, hyperpiesia, intracranial tumors, head injuries, epilepsy, migraine and neuroses. The author feels that no drug can compare with phenobarbital in the treatment of aural vertigo. He and a collaborator have sectioned the eighth nerve in five intractable cases and obtained good symptomatic results.

EDITOR'S ABSTRACT.

LIME DEPOSITS IN THE STRIA VASCULARIS OF THE LABYRINTH. H. ROLLIN, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **138**:1 (March) 1934.

Rollin found three cases in which there was a lime deposit in the stria vascularis of the labyrinth among his collection of human temporal bones prepared in serial sections. One was that of a child, aged 2½ years, who died of pulmonary tuberculosis; another was from a child, aged 6 years, who died of pneumococcic peritonitis, and the third was from a man, aged 59, who died of apoplexy. In none of these patients was disease of the ears known before or during the fatal illness. It was possible to follow in the serial sections the appearance of a diminutive lime deposit, its rapid growth in thickness, width and length, its disappearance and reappearance in another place. The lime deposits in the different serial sections varied from masses the size of a cell nucleus to a lengthy deposit extending along almost the entire stria vascularis. The deposits involved the deeper layers of the epithelium, in which numerous capillary vessels are also found.

The author believes that such deposits develop from the same causes and under the same conditions as those considered by pathologists as the cause of lime processes in the plexus tissue, to which in its anatomic structure and physiologic function the stria vascularis is closely related. Whether the degenerative tissue changes necessary for calcification develop in single cells of the many layered epithelium of the stria vascularis or from the capillaries proper is not definitely determinable. He is inclined to the opinion that the preliminary processes for lime

incrustation lie in degenerative changes of the capillary endothelium, since the capillaries, otherwise numerous, are few in number in the preparations showing calcium deposit.

EDITOR'S ABSTRACT.

TREATMENT OF MASTOIDITIS. MAX MEYER, Jahrb. f. Kinderh. **138**:114 (Jan.) 1933.

This article is a vigorous polemic against Zischinsky, who advised expectant treatment in mastoiditis and otitis media complicating infectious diseases (*Jahrb. f. Kinderh.* **136**:310, 1932).

CLAUSEN, Rochester, N. Y. [AM. J. DIS. CHILD.]

THE DEVELOPMENT OF THE SACCULUS VESTIBULI IN THE HUMAN INNER EAR. J. BRUNNER, Monatschr. f. Ohrenh. **68**:185 (Feb.); 276 (March); 439 (April) 1934.

Brunner describes and discusses in detail the development of the human sacculus vestibuli. The material for this study consisted of enlarged wax models of inner ears of human embryos of varying ages. The original embryos consisted of fifteen varying from 13.6 to 84 mm. in craniococcygeal length. EDITOR'S ABSTRACT.

PATHOGENESIS OF CHOLESTEATOMA OF THE EPITYMPANAL RECESS. F. ALTMANN, Monatschr. f. Ohrenh. **68**:271 (March) 1934.

Altmann describes the accidental observation of a cholesteatoma in a 13 month old boy with marble bones. In both middle ears there was a massive latent hyperplastic infantile otitis with definite disturbance of pneumatization. In the presence of an intact tympanic membrane a small circumscribed cholesteatoma in the recessus epitympanicus had developed. All of the requisites for cholesteatoma formation prescribed by Steurer were present in this case, namely, a mild irritant (latent hyperplastic infantile otitis), a local anatomic predisposition (relatively high mucous membrane covering of the inner surface of Shrapnell's membrane) and, finally, a readiness for proliferation of the epidermis. The question must be considered as to whether the growth was a true cholesteatoma present at birth. Although it is impossible to settle the matter definitely, the author believes this explanation unlikely.

EDITOR'S ABSTRACT.

PHONETICS AND OTOLOGY. E. FRÖSCHELS, Monatschr. f. Ohrenh. **68**:457 (April) 1934.

The effect of disturbances in hearing of various kinds and at different ages on phonetics is discussed by Fröschels. A severe degree of hardness of hearing generally leads only to softening of speech melody and eventuallyl to louder speech than normal or to marked stammering. A parallel development between hearing and the organs of tone takes place. In early childhood from the standpoint of effect on speech it is immaterial whether the hearing injury affects the auditory receptive apparatus or some part of the transmission mechanism. That complete deafness either present at birth or of early development results in dumbness is known. In the course of development of artificial speech in so-called or true deaf-mutes all kinds of stammering defects are developed; the S sounds, for example, are, as a rule, not sharp enough.

Disturbances of musicality are readily affected by disorders of the hearing apparatus. A good musical hearing is dependent on several factors. All tones must be correctly perceived as such. Differences in high notes must be at least qualitatively known. A good memory for correctly perceived tones must exist. Sounds and sound intervals must be correctly heard and remembered. Harmony must be recognized and remembered. Tones following one after another which belong to a melody must be taken in their entirety. In

good hearing the tone levels must be accurately determined. That this may result to some extent from internal accessory perception, perhaps in the tension of the lips, can only be supposed. Many people possess the ability, from tones and from numbers of tones and noises, to hear a portion of quickly successive phonetic pictures. Quickly successive phonetic phenomena are, however, often difficult to to differentiate from each other. It is troublesome to attempt to analyze the single symptoms of stuttering, but it is only in this way that research on stuttering may be freed from a state of lassitude.

EDITOR'S ABSTRACT.

ANOMALY OF THE INCUS-STAPES ARTICULATION AND OF THE STAPES. F. ALTMANN, Monatschr. f. Ohrenh. **68**:469 (April) 1934.

Altmann describes the case of a newly born child whose temporal bone showed chondrodystrophic changes. These changes have been described elsewhere. The tympanic cavities on both sides were of normal size and had normal lumens. The hammer had the usual shape bilaterally, as did the body and short process of the incus. The hammer-incus articulation showed no abnormalities. The long process of the incus was directly connected with the head of the corresponding section of the stapes without intervening articulation. This was present bilaterally. On the right side a connective tissue-bony connection existed by which the long process of the incus formed one continuous bony strand with the head of the stapes. On the left side there was a pure connective tissue binding between the two ossicles. The stapes was abnormally formed on both sides. On the right it was of normal size and formed a lamina; from the middle of the peduncle a stab-shaped process about as long as the peduncle arose; this extended into a headlike swelling above, while below it was slightly widened and bordered a small space. On the left a process rose from the nearly normally formed lamina which in its form and course appeared to represent the anterior pillar; above there existed a headlike enlargement.

In discussing this anomaly the author states that it can be best explained on a developmental basis, being most nearly paralleled by the developmental stage of an embryo of from 16 to 20 mm. Against the origin from chondrodystrophic changes is the absence of similar chondrodystrophic developmental anomalies in many cases of established chondrodystrophy.

EDITOR'S ABSTRACT.

PATHOGENESIS AND TREATMENT OF RETRO-AURICULAR PERSISTING FISTULA AFTER SIMPLE OPENING OF THE MASTOID PROCESS. J. SPIRA, Monatschr. f. Ohrenh. **68**:474 (April) 1934.

Spira believes that the origin of persistent fistulas after simple mastoid operations is dependent on several factors. The principal one is decreased power of repair in the tissues surrounding the operative cavity. This in turn is due to weakening of the entire organism as a result of such a factor as anemia or chronic illness. Accessory causes are of significance, among them the condition of the upper air passages, the anatomic relations of the mastoid process, the time of carrying out the operation and perhaps also the character of the infection. Chronic catarrh of the nose, nasopharynx and accessory sinuses causes retention of the pus in the middle ear and thereby exerts an unfavorable action on the state of the operative cavity. Finally it is known that in patients operated on in a state of recent middle ear inflammation healing is accompanied by the persistence of a fistula behind the ear. Operative technic and postoperative treatment also play some part in fistula formation.

In reviewing his own cases, the author found a decrease in the number of fistulas dating from the time his operative procedure became more radical. The treatment of retro-auricular fistula after simple opening of the mastoid varies. The duration plays an important part. If the fistula is not old and the inflammatory process not yet stopped, it is likely that granulations will still be found. In such cases conservative treatment is best, with all intervention directed toward the stimulation of granulation tissue production. A strengthening diet, good air, change

of climate and general irradiation from a quartz mercury vapor arc lamp may be tried. Roentgen therapy, in the author's opinion, is a complete failure. When the fistula fails to close six months after the operation, further delay is useless and operative intervention is advisable. Several methods have been described and used with varying results. The author has used Passow's method in eight cases; there was complete healing in all.

EDITOR'S ABSTRACT.

MUCOCELE OF THE MASTOID PROCESS; EPIDURAL CHOLESTEATOMA OF THE TEMPORAL BONE. K. AMERSBACH, Ztschr. f. Hals-, Nasen- u. Ohrenh. **35**:272 (March 12) 1934.

Amersbach reports a case of an unusual combination of a pseudocholesteatoma of the middle ear with a directly adjacent (but unconnected) true epidural cholesteatoma. Another patient seen somewhat later showed a similar roentgenographic picture, which caused considerable difficulty in diagnosis. Operation was eventually undertaken, and after the periosteum was separated from the planum mastoideum, a round, blue, shimmering area about 1 cm. in diameter was found, at which point the bone could be indented. This area was removed and examined histologically by Professor Ghon. A polypoid proliferation of the mucosa with hyperemia and nonspecific inflammatory infiltration and massive edematous swelling progressing to pseudocyst formation was observed in all layers. The inflammatory infiltration besides being rich in polymorphonuclear leukocytes showed small mononuclear round cells, many eosinophilic leukocytes and plasma cells. The epithelium was largely cylindrical but also ciliated and contained numerous mucous cells. In this case the initial diagnosis of true epidural cholesteatoma was wrong, as the condition was a mucocele. The clinical and roentgenologic similarity of the two cases discussed indicates the difficulty of preoperative differential diagnosis.

EDITOR'S ABSTRACT.

DEAF AND NONSPEAKING CHILDREN. H. BURGER, Maandschr. v. kindergeneesk. **2**:379 (May) 1933.

Deaf and dumb children of normal intelligence should attend a school for the deaf and dumb, by preference a day-school. If possible, they should enter a preparatory class of the school when they are 3 years old. Children who at first hear and speak and who become totally deaf before the seventh year should attend a school for deaf and dumb children as soon as possible, in order to prevent loss of speech. Deaf and dumb children with weak mentality should not attend a school for mentally defective children, nor should they attend the ordinary class of the school for the deaf and dumb. It would be best to place them in a separate class in an institution for the deaf and dumb and to give them an education in which the dumb show is used. Deaf children aged 3 years with doubtful mental ability should be sent provisionally to a preparatory class of a school for the deaf and dumb. Dumb children 4 years of age and older with hearing and with normal mental abilities should be temporarily placed in a school for the deaf and dumb. If after one or two years they have learned to speak, they should attend the common school. Children who only hear poorly but cannot follow the common school routine should attend a special school for children with deficient hearing.

VAN CREVELD, Amsterdam, The Netherlands. [AM J. DIS. CHILD.]

Pharynx

EFFECT OF TONSILLECTOMY ON THE DEVELOPMENT OF IMMUNITY TO SCARLET FEVER. CAMILLE KERESZTURI and WILLIAM H. PARK, J. A. M. A. **101**:764 (Sept. 2) 1933.

In the limited number of cases studied, tonsillectomy had no marked effect on susceptibility to scarlet fever within six months after it had been done, as demonstrated by the changing of a positive reaction to the Dick test into a negative one.

BONAR, Salt Lake City. [AM. J. DIS. CHILD.]

ON LYMPHO-EPITHELIOMA OF THE NASOPHARYNX AND TONSILS. D. F. CAPPELL, J. Path. & Bact. **39**:49, 1934.

Twelve cases of malignant disease of the nasopharynx, tonsils and pharynx have been studied and are believed to be of epithelial origin, arising from the specialized epithelium of the pharyngeal lymphoid tissues. The value of silver impregnation of the reticulum as a means of demonstrating the structure of such growths is emphasized. These tumors show distinctive clinical and pathologic features and may justifiably be separated from other neoplasms under the name of "lympho-epithelioma." Two main types of histologic structures have been recognized, the one corresponding to the classic lympho-epithelioma of Regaud and the other to the lympho-epithelioma of Schmincke. It is shown that these are not different types of neoplasm but represent merely quantitative differences in the mode of growth and spread of the tumor cells. Evidence for regarding transitional cell carcinoma of the nasopharynx and tonsil as a different form of neoplasm from lympho-epithelioma is not definitely established in the present observations, and it is believed that the two are at least closely related. Lympho-epitheliomas are highly radiosensitive, and the value of radiation therapy in contrast to surgical excision is clearly demonstrated in the present series of cases.

FROM THE AUTHOR'S SUMMARY AND CONCLUSION. [ARCH. PATH.]

A CASE OF NASOPHARYNGEAL TORTICOLLIS. J. GUÉRARD, R. POTVIN and J. B. JOBIN, Bull. Soc. méd. d. hôp. universitaires de Québec **34**:58 (Feb.) 1933.

A girl, aged 9 years, came to the hospital complaining of a red and painful swelling which had appeared two days before in the left nasal ala and had spread rapidly to the left eyelid and then to the entire left side of the face. The temperature rose to 104 and 105 F.; the pulse was feeble, and the patient was stuporous. A few days later the upper eyelid on the left side suppurated and was incised, after which the skin of the entire lid sloughed away. Soon the left side of the scalp and face began to suppurate profusely and became denuded of skin. The septicemia lasted eight months, with slow improvement. During this period osteo-arthritis of a finger of the right hand occurred, with extensive osteoperiostitis of the right femur, osteitis of the right humerus, an abscess of the left lung and a renal complication the presence of which was revealed by pyuria and hematuria. An unusual complication consisted in an inability to rotate the head, which developed during several days and which was characterized by fixity of the head and neck, with massive cellulitis in the latter region, all depending on rotation of the atlas by which one side, usually the left, projected forward beyond the other, and on a cervical curvature of the spine, with the convexity to the right. In this right-sided protrusion could be felt the spinous process of the axis, pushed to the right by the sliding forward of the axis and its rotation to the left. This was brought out by roentgenograms. The condition was diagnosed as naso-pharyngeal torticollis. This disease was first described by P. Grisel in 1930 and has received the name of Grisel's disease. It occurs chiefly in girls from 8 to 12 years of age, following the appearance of an abscess in the retropharyngeal region or other angina of the throat. If it is not recognized and treated, it becomes chronic. In this stage a characteristic sign is the "sternal paradox," meaning that the sternocleidomastoid muscle which contracts tonically is that not of the affected but of the opposite side.

VINTON, Brooklyn. [AM. J. DIS. CHILD.]

THE PROBLEM OF THE TONSILS. T. J. BÜRGERS and W. WOLFHEIM, Klin. Wchnschr. **10**:1064 (June 6) 1931.

An attempt was made to associate pathogenic bacteria obtained from the tonsils with the pathologic processes in those structures. Use was made of the percentile index (Fresszahl), or the proportion of leukocytes taking part in phagocytosis. It was found that in infection of the tonsils the index was low, suggesting low

defensive powers, and that following tonsillectomy the index rose to 50 per cent or more. In cases in which the index was originally around 50 per cent, the authors believe that the tonsils cannot be incriminated or that the defensive mechanism was sufficient to take care of the infection without surgical intervention; further observation is called for, however, because this relationship could readily change.

SILVERMAN, Syracuse, N. Y. [AM. J. DIS. CHILD.]

SEPSIS FOLLOWING ANGINA AND TONSILLECTOMY. JAN HYBASEK, Časop. lék. česk. **71**:993 (Aug. 5); 1034 (Aug. 12); 1078 (Aug. 19) 1932.

The author discusses the various types of tonsillitis from the clinical, etiologic, symptomatic and diagnostic aspect and cites the contemporary literature. He classifies tonsillitis as follicular, phlegmonous, pseudomembranous and vesicular. The therapeutic measures used are outlined. A series of reports of cases is presented, and the prognosis is discussed. The résumé of active treatment is as follows: Drainage in acute sepsis is more important than tonsillectomy. The indications for tonsillectomy should be limited rather than amplified in postanginal sepsis. Peritonsillar abscesses should be opened widely orally, and tonsillectomy should not be performed in the presence of a peritonsillar phlegmon. Prophylactic jugular ligation should not be done, but thrombosed vessels should be ligated or excised. The deep structures of the neck and the parapharyngeal regions should be opened widely and drained. A bibliography is appended.

STULIK, Chicago. [AM. J. DIS. CHILD.]

ROENTGEN TREATMENT OF CHRONIC TONSILLITIS. ERIK WOLFF, Finska läk.-sallsk. handl. **75**:965 (Oct.) 1933.

Pathologic studies of tonsils subjected to roentgen radiation did not show atrophy or other marked changes. No bacteriologic studies were made.

ELGHAMMER, Chicago. [AM. J. DIS. CHILD.]

Larynx

STROBOSCOPY CENTENNIAL. H. STERN, Monatschr. f. Ohrenh. **68**:569 (May) 1934.

Stroboscopy, according to Stern, depends on two laws of physiologic optics: (1) the law that from every light stimulus which reaches the eye a (positive) after-image remains for two-tenths second and (2) the fact that the light stimuli are no longer correctly taken by the rods and cones of the retina if the succeeding period is less than one fifth of a second. If the interval is less than one fifth of a second a confluent and swimming image occurs. Stroboscopy gives evidence of finer motions of the vocal cords which ordinary laryngoscopy fails to reveal. This vibratory ability is dependent on the quality and quantity of the vocal cords, the condition of tension, the elastic quality, the method of function of the expiratory pressure and the geometric form of the cords. As a result of stroboscopic studies, the author proposes a triad of symptoms consisting of: (1) normal laryngoscopic observation with respect to the coarse movements of the vocal cords; (2) stroboscopically demonstrable limitation of the movement of one cord or its complete immobilization (this may involve the entire vocal compass or only a certain tone range), and (3) limitation of the vocal compass or of only a certain range. It is thus possible to determine by the stroboscopic method vocal facts which are not detectable by laryngoscopy.

EDITOR'S ABSTRACT.

ANATOMIC MIRROR PICTURE OF THE MECHANISM OF THE FALSE VOCAL CORDS AND THE RECURRENT NERVE QUESTION. A. RÉTHI, Monatschr. f. Ohrenh. **68**:586 (May) 1934.

In an attempt to further the knowledge of the false vocal cords, Réthi carried out daily observations on patients operated on for removal of tumors of the vocal

cords. He recently examined 2 patients especially carefully and made the observation that the epiglottis at the beginning, before the false vocal cords had fully developed, was deflected down during phonation, while at the same time it approached the midline more and more. In 1 patient the vocal cord that was not operated on remained fixed and motionless in the midline. As a result of complete paralysis of the adductors it did not swing across the midline against the laterally fixed cord that had been operated on. In the other patient the cord that was not operated on swung slowly, in a steplike manner, with increasing excursions against the operated cord. The effect on the false cords was different in these 2 cases. In the case in which the cord was fixed and the wide space between the two cords could not be closed, so that no vocal sounds could be expected, there was complete development of the false cords. In this case the epiglottis turned downward with phonation, and the false cords turned strongly inward; consequently as a result of the pulling together of the stylopharyngeal muscle the mucosa of the hypopharynx raised itself in the form of a wide fold and the arytenoid cartilage tilted inward so that a light crossing of their apexes was visible. With the stronger development of the false cord voice a parallel hypertrophy of the false cords developed. A sphincter-like pulling together of them could be observed. In the other case, in which the adductors remained functioning at the beginning, no motion of the vocal cords could be observed, the excursions being only slow and steplike.

The action of the two aryepiglottic muscles is naturally sphincter-like. The muscles affecting the larynx can be divided into four groups. The first is the group of small intralaryngeal muscles supplied by the recurrent nerve—the lateral crico-arytenoid muscle, the thyro-arytenoid muscle and the transverse muscle. These are supplied solely by the inferior laryngeal nerve. The cricothyroid muscle is supplied by the outer branch of the superior laryngeal nerve. These two groups form the system of true phonation muscles. The remaining two groups are the outer laryngeal muscles and the stylopharyngeal muscle system. The last mentioned group under pathologic conditions plays the rôle of a substitution phonation muscular system by development of the false cord voice. This division explains why in some cases of paralysis of the recurrent nerve the median position, and in others the intermediary, is seen.

EDITOR'S ABSTRACT.

INDICATIONS FOR ACTIVE TREATMENT OF LARYNGEAL TUBERCULOSIS. C. AROLD, Ztschr. f. Laryng., Rhin., Otol. (Teil 1: Folia oto-laryng.) **25**:131, 1934.

Arold states that the indications for active treatment of laryngeal tuberculosis are not clearcut. Thus it has been noticed that in spite of a relatively stationary pulmonary condition and an unsettled general condition, active treatment of the larynx often is poorly tolerated. On the other hand, in the presence of an active process in the lungs the treatment sometimes has the desired result. It is therefore apparent that the basis for active treatment is to be sought not in the general condition but in some special reactive state of the organ. In order to attempt estimation of this reactive state, the author made observations on the white cell count of the blood. On analytic comparison of the course of the laryngeal process and the white blood cell count and of the pulmonary process and the erythrocyte sedimentation rate, it was apparent that there is a parallelism of the former two and of the latter two. Naturally one white cell count is insufficient, but the author believes that from two to three weeks of control of the blood is sufficient. Only when the blood count is normal on such observation does active treatment of the larynx come into consideration. Thus, especially in the case of a circumscribed focus, treatment with gold salts and roentgenotherapy or other radiation therapy is desirable. If, under these circumstances, failure results from active treatment, it is more often due to the choice of method than to the indications. The danger, however, is not serious.

EDITOR'S ABSTRACT.

Nose

SINUSITIS IN CHILDREN. HENRY A. REISMAN, Arch. Pediat. **50**:795 (Nov.) 1933.

The general subject of sinusitis in children is discussed, and attention is particularly called to the enlargement of the submaxillary glands as an aid to early diagnosis. WADDELL JR., University, Va. [AM. J. DIS. CHILD.]

FURTHER OBSERVATIONS ON THE SPHENOPALATINE GANGLION. D. STEWART and V. LAMBERT, J. Laryng. & Otol. **49**:319 (May) 1934.

In a previous communication Stewart and Lambert expressed doubt that the sphenopalatine ganglion could be the cause of the many disorders which had been attributed to it. Since that report (October 1930) they have carried out clinical investigations of the problem on four groups of patients: (1) symptom-free patients used as controls, (2) patients with typical headache of the lower half of the head, (3) patients suffering from disorders of the nasal vasomotor system and (4) a composite group consisting of patients with neuralgic pains in the region of the head and neck without any recognizable causative lesion. It was felt that if cocainization of the neighborhood of the ganglion produced such a striking modification of function of the nervous mechanism, simultaneous changes would be recognizable in the areas controlled by the nerves involved in the nature of anesthesia or paresthesia. All of the patients, including the controls, were first tested by means of the algesimeter according to the accepted method. A cocaine-epinephrine solution was then applied to the sphenopalatine foramen, which lies on the lateral nasal wall opposite the posterior end of the middle turbinate.

The authors concluded that cocainization of the foramen forms a quick and efficient method of producing temporary anesthesia of the nasal cavity. Afferent impulses from local lesions in the superior division of the fifth nerve may be blocked by a local application to the sphenopalatine foramen. As a result, painful conditions in this region which produce referred pains at a distance can be controlled. No evidence was found to support the view that there are afferent sympathetic fibers present in the nerves considered. EDITOR'S ABSTRACT.

NASAL POLYPS. L. LEROUX and J. DELARUE, Ann. d'anat. path. **10**:879, 1933.

The authors classify nasal polyps into four groups. Each group is characterized by certain clinical and histologic features. 1. Inflammatory nasal polyps are composed of inflammatory granulation tissue, often very vascular, with extensive round cell and plasma cell infiltrations. This form has as its background a chronic infection, usually of the accessory nasal sinuses. 2. Edematous nasal polyps, the stroma of which is edematous, present a pseudomyxomatous picture. They are found in patients with vasomotor and sympathetic instability, vasomotor rhinitis, etc. 3. A third group of polyps has an extensive infiltration of the stroma by eosinophil leukocytes. This form occurs in patients with asthma and other allergic phenomena. 4. The tumor polyps may be composed of either a glandular or an epithelial proliferation; rarely an angiomatous picture is seen, but in the latter case the polyp is usually on an inflammatory basis.

PERRY J. MELNICK. [ARCH. PATH.]

SYNDROME OF THE NASAL NERVE. WIBO, Ann. d'ocul. **170**:169 (Feb.) 1933.

In a study of neuritis of the nasal nerve, Wibo enumerates the characteristic features as follows: (1) a well marked inflammatory lesion of the anterior segment of the eye; (2) severe neuralgic pains in the orbitonasal region of the same side, but with elective localization at the root of the nose and in the ala on the side corresponding to the inflamed eye; (3) a copious hydrorrhea, which accompanies

the paroxysmal crises. Only an accurate knowledge of the anatomy of this region can clarify the symptomatology of this disease. After having eliminated various diagnoses, Wibo suggests that the cause is neuritis of the nasal nerve. Cocaine and epinephrine applied to the nose produce rapid and complete relief.

BERENS, New York. [ARCH. NEUROL. & PSYCHIAT.]

ACUTE ETHMOIDITIS WITH CELLULITIS IN THE COURSE OF SCARLET FEVER; INTERVENTION; CURE. BABONNEIX, HALPHEN and WILM, Bull. Soc. de pédiat. de Paris **30**:583 (Nov. 15) 1932.

A boy, 5 years old, with scarlet fever had a swelling on the left side of the bridge of the nose, edema of the left eyelids and exophthalmos of the left eye. The nasopharyngeal cavity had been the seat of infection for a long time. Roentgenologic examination revealed cloudiness of the left ethmoid and maxillary sinuses. These were explored surgically; the mucous membrane lining them was inflamed, and there was cellulitis of the surrounding tissues; no frank pus was located. The child made an uninterrupted recovery and left the hospital a month after the operation.

BERENS, New York. [ARCH. NEUROL. & PSYCHIAT.]

THE SUBPERIOSTEAL, VESTIBULONASAL OPERATIVE METHOD: A NEW OPERATIVE PROCEDURE FOR THE NASAL ACCESSORY SINUSES. E. MATIS, Monatschr. f. Ohrenh. **68**:307 (March) 1934.

The subperiosteal vestibulonasal operation for disease of the frontal sinus, empyema and pansinusitis has previously been described by Matis. Since the former publication he has extended the technic, which is described in this paper. He describes the instruments used, the anesthetic (local), the operative incision, the subperiosteal loosening of the soft parts, the resection of the frontal process and, finally, the operative procedures for involvement of different sinuses, i. e., disease of the frontal, ethmoid or sphenoid sinus, respectively, combined empyema and pansinusitis. One of the most important advantages of this method of dealing with a diseased frontal sinus is the absence of facial scarring such as occurs with the external operation. The entire healing process is more rapid, and there is less reaction than by open operation. The tendency to stenosis of the communication between the frontal sinus and the nose, well known after the external operation, does not occur in patients operated on by the author's method. The absence of postoperatively painful scars is a further advantage. In regard to recurrences, the author believes that insufficient time has as yet elapsed in which to draw comparative conclusions.

AUTHOR'S ABSTRACT.

Miscellaneous

SPEECH DISORDERS OF PHYSICAL ORIGIN. JOHN A. GLASSBURY, Arch. Pediat. **50**:802 (Nov.) 1933.

Glassbury believes that treatment of disorders of speech is peculiarly a medical problem, and classifies and discusses some of the common disturbances of speech. He classifies stammering as a neurosis of speech coordination based on a mental conflict—a definite pathologic condition. He thinks that defective formation of words, with the exception of a foreign accent and improper pronunciation, should be considered as based on physical and often remedial causes.

WADDELL JR., University, Va. [AM. J. DIS. CHILD.]

SPEECH DISORDERS AS A MEDICAL PROBLEM. SMILEY BLANTON, New York State J. Med. **33**:215 (Feb. 15) 1933.

As speech is one of the highest functions of human organization it is also one of the best indicators of the state of development of the central nervous system, especially the brain. Defects in speech due to organic lesions of the brain are seen in multiple sclerosis, dementia paralytica and hemorrhage of the brain. They are also found in myasthenia gravis.

Little's disease is frequently accompanied by slurring or indistinct speech. In such cases training in speech should be in small doses and should be carried out over some time. Such training should be supervised by the physician to avoid overtreatment. The child who does not talk at the age of 2 or 2½ years may have a defect. The most common cause of delayed speech in children is amentia due to lack of brain development. Minute hemorrhages at birth or later encephalitis may be the cause. The attention of such children is too fixed. The normal child does not fix his attention on one thing for a long time. The correction of defects in speech due to deafness requires teachers experienced in the training of the deaf.

Sometimes indistinct and slurring speech is found in bright children, owing to oral inactivity. Severe illness between the fifteenth and twenty-fourth months may cause retardation in speech. Tonguetie is rarely the cause. Defects in speech are often used by children as a means of dominating parents and nurses. The substitution of "th" for "s" may be due to the desire to remain an infant. Children who show this tendency should not be given things that they desire until they say the words clearly and distinctly.

Stuttering is caused by emotional factors, such as timidity or anxiety. From 5 to 10 per cent of nursery children stutter for a period; 2 or 3 per cent stutter for several months, and 1 per cent of the general population stutters. Exercises in speech should not be used for young stuttering children. Better results are obtained by a change of environment. Remove pressure, demand less response in speech and give the child more freedom. Teach the child to adjust himself to situations through games, plays and mental hygiene. Build up a feeling of confidence and security. By modification of personality tendencies, such as marked anxiety, sensitiveness or overagressiveness, defects in speech can be eliminated.

AIKMAN, Rochester, N. Y. [AM. J. DIS. CHILD.]

CARCINOMA OF THE OESOPHAGUS TREATED BY RADIATION. F. J. CLEMINSON and J. P. MONKHOUSE, J. Laryng. & Otol. **49**:313 (May) 1934.

The material on which this study by Cleminson and Monkhouse was based consisted of all the patients with carcinoma of the esophagus treated in the throat department of the Middlesex Hospital during the years 1925 to 1932. In all there were eighty-nine patients, seventy-nine men and ten women. The general mode of treatment consisted in esophagoscopy for diagnosis, with removal of a fragment of the growth for section, and examination of the patient with the roentgen rays to determine the length of the stricture (Trendelenburg position). From this information the dose of radon to be used and the length of the applicator were decided. At a second esophagoscopy the radon was placed in position and left for seven days. The average survival period for the whole series was 5.6 months. For the ten women it was 8.5 months, and for the seventy-nine men, 5.2. The average duration of dysphagia, according to the history, was 5.4 months for the women and 3.8 for the men. Thus women had both a longer history and a longer survival period. One patient treated solely by roentgen rays with a survival period of ten months was included. The results of treatment were so disappointing that the authors wonder whether it is not actually harmful to treat these persons by the application of radon to the center of the growth and whether they might not live longer if the only treatment were preliminary removal of all teeth, followed by gastrostomy. There may even be a certain danger of stimulation of the rate of growth at the periphery, and thus the end may be hastened rather than delayed. Perhaps, however, this series is too small to permit the results to have more than a suggestive value.

EDITOR'S ABSTRACT.

TRACHEOBRONCHIAL CROUP, PROBABLY STREPTOCOCCIC; CURE BY TRACHEOTOMY AND BRONCHOSCOPY. CAYLA, BUNEAU and WILM, Bull. Soc. de pédiat. de Paris **30**:681 (Dec. 20) 1932.

A boy, 6 years old, who had been immunized against diphtheria two years previously, had laryngitis and tracheobronchitis. He was on the point of suffoca-

tion when intubation was tried; he stopped breathing and became markedly cyanosed, so that immediate tracheotomy was done. After five minutes of artificial respiration and administration of oxygen he recovered. The following day he had marked dyspnea which was not relieved by cleaning of the tracheal cannula and removing as much membrane as was possible through the tracheotomy opening, so a bronchoscope was inserted and by means of a forceps the trachea was cleaned of all membrane as far as the bifurcation. The child improved, and the tracheal tube was removed four days later without subsequent trouble. No diphtheria bacilli were grown in repeated cultures made from the membrane, but a pure growth of streptococci was obtained. Repeated doses of diphtheria antitoxin were administered, even though the child had been ill for six days when he was admitted to the hospital and despite cultures negative for Bacillus diphtheriae. When membrane extends beyond the larynx, bronchoscopy is indicated.

BENJAMIN, Montreal, Canada. [AM. J. DIS. CHILD.]

RESULTS WITH A KERATIN DERIVATIVE (DETOXIN) IN INFLAMMATORY PROCESSES AND SEPTIC CONDITIONS OF OTORHINOLARYNGOLOGY. MARIA SVERAK, Monatschr. f. Ohrenh. **68**:411 (April) 1934.

Sverak discusses the use of a keratin preparation derived from the skin and connective tissue, the effect and toxin-combining power of which are due to its content of amino-acid and organically combined sulphur. Two methods of injection may be used, she says, the intravenous and the intramuscular, but 10 cc. single doses should not be exceeded. A chill often develops after intravenous injection, but good results on the course of the infection and fever are usually observed after one or two injections. In reporting the results of this treatment on a number of patients with infections of the upper respiratory passages or ears, she expresses the belief that this substance not only causes early circumscribed infectious processes to heal but prevents septic complications. Moreover, in cases in which an operation cannot be performed, this preparation may decrease the severity and shorten the course of the illness. In none of her cases in which the patients were treated with this substance did further complications occur, even when indications for their development were present. EDITOR'S ABSTRACT.

SPEECH DEFECT: GENERAL CLASSIFICATION; ASSOCIATIVE APHASIA. ALEXANDRA STEPOWSKA, Pedjatrja polska **12**:485, 1932.

Speech defects are due to pathologic conditions. These conditions can be systemic, local or functional. The speech reflex as described by Lichtheime and Wearnicki is as follows: The sounds are received by the hearing apparatus and transmitted to the Wernicki center, where sounds are recorded and impressed; understanding of speech, association of objects and remembrance of words and their significance become located in the transcortex; from there the impulse is transmitted to the Broca center, then to the nucleus of the motor nerves located in the fourth ventricle, pons Varolii and rhomboid fossa, and then to the nerves supplying the tongue, lips, palate and posterior part of the throat. This scheme is often questioned by new investigators. Speech defects are classified, according to the Vienna schools, as follows:

A. Dumbness: (*a*) surdo mutitos, or state of being deaf and dumb; (*b*) mutitos idiotatica, and (*c*) mutitos imbecillitatis
B. Aphasia (loss of speech previously present)
C. Dyslalia (defect in pronunciation of certain sounds)
D. Associative aphasia, such as stammering, stuttering and faltering
E. Systemic speech defect, as in disseminated sclerosis, bulbar paralysis and chorea
F. Speech defect in mental disorders.

KRUPINSKI, Chicago. [AM. J. DIS. CHILD.]

Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OTOLARYNGOLOGY

WILLIAM HEWSON, M.D., *Recorder*

May 16, 1934

THE EDUCATED VOICE FROM A MEDICAL AND ECONOMIC POINT OF VIEW. DR. CHARLES P. GRAYSON.

By the educated voice is meant one notable for its purity of tone, with no suspicion of dryness; it flows smoothly and has no sudden changes of pitch or power; its quality shows that there is no muscular intereference. It uses to fullest advantage the resonance given to it by the several resonating cavities; it contains the complete series of overtones, and, finally, it is flexible. Such a voice can be still further enriched if there is associated the artistic temperament. Such a seeming idealization of the human voice is possible.

The education of the voice should be begun in early youth. The earlier the speaking voice is trained in correct enunciation, in intonation and, most importantly, in control of the volume, the easier it will be later to develop the singing voice.

The economic value of an even moderately well developed voice and its value as a bread-winning asset are little inferior in importance to the value of good vision and hearing. Early instruction in the proper use of the voice largely prevents the fatiguing strain to which the vocal cords and their muscles are so frequently exposed and the repeated hyperemias and congestions which lower their resistance and make them the victims of catarrhal inflammation.

If a child is taught the habit of doing his talking, laughing and crying in what may be called the middle or natural voice he will enter youth and maturity with an uninjured and resistant laryngeal mucous membrane.

The connection between the reproductive system and the larynx is by no means certain, but the maturing of the two is coincidental. Within a few weeks of the completion of the work the larynx as a whole has increased in all its dimensions, and the vocal cords have gained in length, breadth and thickness. During the period of readaptation of the cords and muscles to their more roomy quarters, every now and then their tension weakens for an instant and the voice breaks.

Children mimic their elders successfully in many ways, and if born into a family environment of educated voices they will adopt the vocal models surrounding them. From such families one does not draw laryngeal patients. It is in members of families of the opposite type, which from dawn to darkness seem determined to outshout each other, that one sees the whole upper air tract in a state of smouldering congestion or hyperemia, requiring little to start an acute inflammation. Therefore, is it not one of the responsibilities of the otolaryngologist to enlighten adults and children as to the cumulative risk that they run by the harmful straining of their voices?

CONGENITAL WEB OF THE LARYNX. DR. GABRIEL TUCKER.

This article will be published in full in a later issue of the ARCHIVES.

DISCUSSION

DR. F. O. LEWIS: I am very much interested in Dr. Tucker's case. I have not had a patient of this type, but I recently saw a patient with a web at the level of the second or third ring of the trachea, which was apparently congenital and because of the symptoms was being treated for asthma. He had had a number

of serious attacks of dyspnea and was examined by a number of laryngologists from neighboring towns, but no obstruction was demonstrated. The web was more or less concentrically placed and the lumen reduced about two-thirds. The patient's condition was so alarming that tracheotomy was necessary. Following this, probing of the web showed that it was quite thin. With a punch forceps several pieces were removed. The patient made a satisfactory recovery.

ROENTGENOTHERAPY FOR OTORRHEA FOLLOWING RADICAL MASTOIDECTOMY. DR. LOUIS H. WEINER.

While otolaryngologists recognize that a cessation of aural discharge following a radical mastoidectomy is not an indication of success or failure, it is nevertheless considered so from the patient's point of view.

The peculiar anatomic and histologic structure of the temporal bone and middle ear often lends itself to a persistent otorrhea. At operation it is impossible to remove all of the mucous membrane of the tympanic cavity. Kopetzky and others have stated that it is necessary to remove the linings not only of all diseased cells but of the healthy ones, as otherwise irregularity of the newly formed epithelium will produce persistent drainage pockets. Secondary infection often occurs in granulation tissue of the mastoid portion of the tympanic cavity. Patients failing to report after radical mastoidectomy have moist cavities with exuberant granulations. Failure to remove the tegmen tympani, according to Ballance, is a great source of recurrent disease. Persistence of adenoid tissue in adults may cause the condition to continue. Graham observed many cases of persistent otorrhea due to constitutional disease.

The principles of treatment of persistent otorrhea following the radical operation emphasize the eradication of the focus. This focus may be caries or a cholesteatomatous infiltration located in the attic, aditus or antrum. The operation which eradicates this focus is successful, despite a possible resultant persistent discharge. Mygind, one of the leading advocates of general medical treatment, contends that there is a disturbed water metabolism in these cases. He obtained excellent results in refractory cases with the "thirst" cure and ordinary stimulative treatment. The literature abounds with various methods of local treatment. It often becomes necessary to pursue a variety of procedures in order to obtain a dry ear. Zinc and copper ionization, the use of iodine dusting powder, ultraviolet irradiation endoaurally with a quartz applicator and the application of boro-alcohol and Calot's solution are suggested for local treatment. (Calot's solution is made up as follows: guaiacol, 0.00025 Gm.; creosote, 1.5 Gm.; iodoform, 3 Gm.; ether, 8.5 cc., and olive oil to make 1 ounce [29.5 cc.].)

Roentgenotherapy has succeeded in cases in which the other methods mentioned had failed. The technic as suggested by Dr. Barton R. Young, of Temple University, was: Fifty roentgens were applied to the ear twice weekly for two or three months, depending on results. A small area was used, and the rays were directed at the external auditory meatus, the dosage being 160 kilovolts, 50 cm. target skin distance, with a 1.2 mm. copper and a 1 mm. aluminum filter, for two and one-half minutes. The ear was thoroughly cleansed, dried and packed with plain gauze first, the roentgenologist removing the packing prior to his treatment. The patient was immediately referred back to the otologist, who in turn again cleansed, dried and firmly repacked the aural canal with plain gauze. An average of eight treatments were required. The patient was instructed to apply pressure in rapid succession, with the index finger over the tragus. These massages stimulated epithelial growth. Fifteen patients with persistent otorrhea have been successfully treated by this method. The patient treated first has had a cessation of the aural discharge for a year and a half; the one treated most recently, for three months.

The x-ray has a peculiar affinity for embryonic tissue, and the dosage has been so well established that one can destroy the embryonic granulation tissue without disturbing the epithelial ingrowth. Massaging the ear stimulated epidermatization. The packing in the interim further prevented granulation tissue formation.

DISCUSSION

DR. MATTHEW S. ERSNER: Several problems confront one in treating patients after radical mastoidectomy. In some cases there seems to be no cessation of discharge, and in some the discharge is even made worse, so that one tries one thing after another, to find that what benefits one patient will have no effect on the next one. It is said by philosophers that it is useless to look back, but roentgenotherapy offers something of real value. Dr. Weiner called attention to "our enemy the connective tissue." Where my associates and I have failed in our treatment we have found a growth of granulation or connective tissue. In such cases a covering is needed, so we use a skin flap or a Thiersch flap; nature seems to want an ectodermal protection. Though there are only fifteen cases in which we have tried this method, we feel that we have tried all the other methods and failed and that roentgen therapy offers the best solution to the problems.

DR. GEORGE M. COATES: Many points in this paper lend themselves to discussion. Dr. Ersner is right in assuming that nature's tendency to protect underlying tissue is by epidermatization. While the performance of the radical mastoidectomy is not difficult, one does not obtain dry ears. One New York otologist reported 100 per cent dry ears, but Dr. Harris told me that he had frequently seen patients of this operator and others who showed discharging ears. Logan Turner, at a meeting of the Royal College of Surgeons, reported that 80 per cent of his patients had dry ears, but that ears were considered cured in spite of their wetness. There is no doubt that more radical mastoidectomies would be done if one could assure the patients dry ears. Any method that will aid in this is of interest to all otolaryngologists. I think that this method as presented is therefore encouraging. The presence of exuberant granulation tissue is evidently the cause of the failures.

Book Reviews

Clinical Pathology of the Jaws, With a Histologic and Roentgen Study of Practical Cases. By Kurt H. Thoma, D.M.D., Bracket Professor of Oral Pathology in Harvard University. Price, $9. Pp. 643, with 423 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

This is a volume of six hundred and forty-three pages, with a large number of illustrations of gross and microscopic preparations, as well as roentgenograms. The diseases of the jaws represent a field of borderline conditions, a "no man's land," which concerns especially the dental surgeon, the general surgeon and the general practitioner, as well as the physician who is limiting his field to the practice of otolaryngology. The author drew material from the Laboratory of Oral Pathology of the Harvard University Dental School, as well as from the Boston hospitals—Boston City Hospital, Massachusetts General Hospital and Peter Bent Brigham Hospital.

The volume represents an exhaustive study, with numerous references to the literature. It will serve as a valuable reference work for the general practitioner, the oral surgeon and the dentist.

News and Comment

AMERICAN BOARD OF OTOLARYNGOLOGY

An examination was held in San Antonio, Texas, Nov. 13, 1934, during the meeting of the Southern Medical Society. Twenty-five candidates were examined, of which number seven were conditioned or failed.

During 1935, examinations will be held in New York on June 8, in connection with the meeting of the American Medical Association, and in Cincinnati in the fall, during the meeting of the American Academy of Ophthalmology and Oto-Laryngology. Applications for certificate should be addressed to the secretary, Dr. W. P. Wherry, 1500 Medical Arts Building, Omaha.

ATLANTIC CITY SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The Section on Laryngology, Otology and Rhinology of the American Medical Association has appointed the following section exhibit committee for the scientific exhibit at the Atlantic City Session of the American Medical Association and the Canadian Medical Association: William V. Mullin, Cleveland, chairman; Austin A. Hayden, Chicago; John J. Shea, Memphis, Tenn., and Gregor McGregor, Toronto, Canada. Application for space must be made by Feb. 25, 1935. Application blanks may be obtained from any of the members of the committee or from the Director, Scientific Exhibit, 535 North Dearborn Street, Chicago.

Directory of Otolaryngologic Societies *

FOREIGN

Collegium Oto-Rhino-Laryngologicum Amicitiæ Sacrum

President: Prof. Gunnar Holmgren, Karolinska Mediko Kirurgiska Institut, Stockholm, Sweden.
Secretary: Prof. Dr. C. E. Benjamins, Verlengde Heereweg, 143, Groningen, The Netherlands.

NATIONAL

American Medical Association, Scientific Assembly, Section on Laryngology, Otology and Rhinology

Chairman: Dr. John J. Shea, 1018 Madison Ave., Memphis, Tenn.
Secretary: Dr. John W. Carmack, 23 E. Ohio St., Indianapolis.
Place: Atlantic City, N. J. Time: June 10-14, 1935.

American Academy of Ophthalmology and Otolaryngology

President: Dr. J. M. Wheeler, 30 W. 59th St., New York.
President-Elect: Dr. Wells P. Eagleton, 15 Lombardy St., Newark, N. J.
Executive Secretary: Dr. William P. Wherry, 1500 Medical Arts Bldg., Omaha.
Place: Cincinnati. Time: 1935.

American Bronchoscopic Society

President: Dr. Henry Hall Forbes, 40 E. 61st St., New York.
Secretary: Dr. Lyman Richards, 319 Longwood Ave., Boston.

American Laryngological Association

President: Dr. Dunbar Roy, 113 N. Pryor St., Atlanta, Ga.
Secretary: Dr. W. V. Mullin, 9204 Euclid Ave., Cleveland.

American Laryngological, Rhinological and Otological Society, Inc.

President: Dr. Perry G. Goldsmith, 170 St. George St., Toronto, Canada.
Secretary: Dr. R. L. Loughran, Bridgewater, Conn.

SECTIONS:

Eastern.—Secretary: Dr. Vernon L. Bishop, Medical Arts Bldg., Rochester, N. Y.
Southern.—Secretary: Dr. E. G. Gill, 711 S. Jefferson St., Roanoke, Va.
Middle.—Secretary: Dr. Frank J. Novak, Jr., 30 N. Michigan Ave., Chicago.
Mid-Western.—Secretary: Dr. Arthur W. Proetz, Beaumont Bldg., St. Louis.
Western.—Secretary: Dr. Fred. H. Linthicum, 941 Pacific Mutual Bldg., Los Angeles.

American Otological Society

President: Dr. S. J. Crowe, Johns Hopkins Hospital, Baltimore.
Secretary: Dr. Thomas J. Harris, 104 E. 40th St., New York.

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* Secretaries of societies are requested to furnish the information necessary to keep this list up to date.

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